

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

## Herbal Drug–Induced Liver Injury



Martin Tagle, MD  
Gastroenterologist/Hepatologist  
Gastro Health  
Miami, Florida

### G&H What percentage of cases of liver injury are caused by herbs or herbal drugs?

**MT** Several registries around the world record cases of drug-induced liver injury. The US Drug-Induced Liver Injury Network (often referred to as DILIN) has recorded more than 839 cases of liver injury, approximately 10% of which are caused by herbs. Recently, Dr Fernando Bessone, Dr Nelia Hernandez, and other hepatologists in Latin America established the Latin American Drug-Induced Liver Injury Network (known as LATINDILIN) in collaboration with a Spanish registry. These and other doctors, including myself, have prospectively collected more than 350 cases of drug-induced liver injury, of which 29 (>8%) were caused by herbs. Thus, herbal drug–induced liver injury is quite common.

### G&H Which herbs and herbal drugs are the most common causes of liver injury?

**MT** Our research in Latin America found the most common causes to be *Camellia sinensis*, which is the active compound of green tea, and Herbalife products, which contain a mixture of herbs (although it is not known which herb[s] can cause liver injury). These herbal products are perceived to be innocuous and healthy, and are often thought to be beneficial for weight loss, but that is not the case. They can induce autoimmunity and frequently cause injury of the liver. Another herb that can cause liver injury is *Garcinia cambogia*, which is especially popular in Argentina and is sold by health food stores as well as on websites such as Amazon. Other herbal causes of liver injury include *Ginkgo biloba* and kombucha tea, which is very popular, particularly in Peru.

Interestingly, these liver injuries are not caused by ingesting a set amount of these herbal products. These

injuries are known as idiosyncratic reactions, which are not related to the quantity of an herbal product. They are unexpected reactions to usual portions of the product. Any person with any amount may be susceptible to developing such an injury.

### G&H What are the most common presentations of herbal drug–induced liver injury?

**MT** Most cases are asymptomatic and present only with elevated liver enzymes. In a study that my colleagues and I recently published on the Latin American registry, we also found a high frequency of jaundice, which is an alarming symptom because it is an indicator of severe liver injury. Of the 29 patients who had herbal drug–induced liver injury in the registry, 19 had jaundice. In the Spanish and US registries, almost two-thirds of the patients required hospitalization. In contrast, only 40% of patients with herbal drug–induced liver injury in the Latin American registry were hospitalized. However, the low hospitalization rate may be because of decreased access to health care in Latin America compared with the United States or Europe. Patients with liver injury caused by herbal drugs may have severe liver failure and may even die. In fact, 2 patients in the Latin American registry died, and another 2 patients needed a liver transplant. Thus, presentations of herbal drug–induced liver injury can vary widely, from almost no symptoms with only liver enzyme elevation to jaundice, liver failure, and death.

### G&H What risk factors appear to be associated with this type of liver injury?

**MT** Most patients (almost two-thirds) in the US, Latin American, and Spanish registries have been women. That

may be because women are more prone to consuming herbal drugs than men.

Another likely risk factor is autoimmunity, and women are more prone to having autoimmune-type phenomena. Herbal drug–induced liver injury can mimic autoimmune liver disease. In fact, approximately 20% of cases of herbal drug–induced liver injury present with autoantibodies that can mimic autoimmune hepatitis. At the beginning of these cases, there is no way to distinguish whether the liver injury is caused by herbs/herbal drugs or an autoimmune disease. The key difference is how the patient's liver injury responds to corticosteroid therapy. After such treatment, herbal drug–induced liver injury does not appear again, unlike liver injury caused by autoimmune disease. In the latter scenario, once corticosteroid therapy is withdrawn, the disease returns.

### **G&H** How does the liver injury caused by herbal drugs compare with the liver injury caused by conventional drugs?

**MT** The pattern of liver enzyme alteration seen with herbal drug–induced liver injury is more frequently hepatocellular (aminotransferase elevation). With liver injury caused by anabolic steroid therapy, which is a very common cause of conventional drug–induced liver injury, the pattern is more cholestatic. In the same way, liver injury caused by antibiotics, most commonly amoxicillin and clavulanic acid, typically causes a cholestatic pattern.

### **G&H** What are the possible mechanisms behind herbal drug–induced liver injury?

**MT** The possible mechanisms are not clear, but based upon clinical findings and the mimicry of autoimmune disease, one of the postulated mechanisms is immune-mediated liver damage. That is all that is known right now. The aforementioned herbs, via unknown mechanisms, trigger an autoimmune response—mediated by T-cell lymphocytes—that attacks hepatocytes.

### **G&H** How can liver injury caused by herbal drugs be best diagnosed?

**MT** It is a very difficult diagnosis to make. The clinician has to have a very high index of suspicion and obtain a thorough clinical history, taking into account all of the medications the patient has taken over the previous 3 months. At the beginning of the consult, patients often do not mention that they are taking herbal drugs because they perceive them to be natural remedies and do not consider them to be drugs. Thus, the clinician should insist and ask again if necessary if patients have

taken these specific products. There is no specific test to diagnose herbal drug–induced liver injury; only clinical suspicion and patient history can establish the diagnosis. Almost all causes of acute or chronic liver injury should be considered after a careful patient history and physical examination. For example, acute and chronic viral hepatitis, autoimmune hepatitis, Wilson disease, alpha-1 antitrypsin deficiency, hemochromatosis, alcohol abuse, and celiac disease are conditions that should always be in the differential diagnosis. The coexistence of one of these conditions with superimposed herbal drug–induced liver injury should also be taken into account.

### **G&H** How should this type of liver injury be managed?

**MT** It depends on the case. If a patient has mild to moderate elevation of liver enzymes and does not have jaundice or signs of hepatic encephalopathy or more severe liver damage, management is conservative and consists of withdrawal of the agent, observation, and periodic checking of liver enzymes. However, if the patient develops jaundice or any sign of liver failure, he or she should be hospitalized for close observation. In some cases, depending upon the clinical course, the patient should be evaluated by a liver transplant team. There is no specific medication that should be prescribed. If the patient has evidence of autoimmunity based upon autoantibodies detected in blood, a trial of corticosteroids is reasonable with close monitoring of the patient. If the patient's liver injury responds, the corticosteroids should be withdrawn. If the patient does not relapse off corticosteroids, it is reasonable to diagnose the patient with herbal drug–induced liver injury. It can sometimes take several months to determine that the liver injury has been caused by herbs.

### **G&H** Is it always necessary to completely stop use of the injurious herbal drug?

**MT** Absolutely. These products are never necessary anyway. People take them only because they heard about them from nonmedical sources. As hepatologists, we should always advise that patients stop all unnecessary drugs, starting with herbal compounds.

### **G&H** If the injurious herbal drug is discontinued, is the liver injury usually reversible?

**MT** Fortunately, the liver injury is reversible most of the time. It usually has a benign course. The rates of death and need for liver transplant are not very high. Most cases

typically resolve spontaneously with just observation after stopping the herbal drug that caused the injury.

Some patients choose to undergo a rechallenge to determine whether the product was the actual cause of the liver injury. If a second injury (eg, liver enzyme elevation) is caused by restarting the herbal drug, it is safe to conclude that it is the cause of the liver injury. However, I do not recommend performing a rechallenge; I think it is sufficient to merely stop the herbal drug and never take that compound again.

### G&H Are there any differences in herbal drug–induced liver injury in Latin America compared with other areas?

**MT** The pattern of liver injury is the same (hepatocellular as opposed to cholestatic), and it is predominately female and with a high incidence of autoimmunity regardless of the area. However, Latin America has a low number of cases; considering the large populations in Mexico, Brazil, and Argentina, there should be more cases. It is important to keep in mind that the number of cases depends on whether physicians report their findings. It is likely that there are more cases of drug- and herbal drug–induced liver injury in Latin American hospitals, but they are not being reported. Cases of suspected drug-induced liver injury in Latin America are placed into a database and discussed by the leaders of the registry. It is not easy to report herbal drug–induced liver injury; the physician has to perform a good deal of laboratory workup and rule out other causes of liver injury as previously discussed. Some hospitals are poor and do not have the resources to check for basic viral or autoimmune markers, resulting in underreporting.

### G&H Do you have any advice for doctors managing patients with suspected herbal drug–induced liver injury?

**MT** Every physician, regardless of specialty, should ask patients about all of the medications they are taking, including herbal ones. In addition, physicians should discourage the practice of taking herbal drugs because of the potential harm. When faced with a suspected case of herbal drug–induced liver injury, physicians should refer the patient to a liver specialist for monitoring.

### G&H What are the most important next steps in research in this area?

**MT** Currently, it is difficult to determine the specific cause of molecular mimicry in the T-cell population; thus, having markers that can do so in the future would be helpful. Presently, the research in this area is too preliminary to be useful for clinical practice. In addition, the Latin American registry needs to increase its number of cases of herbal drug–induced liver injury. We should encourage physicians not only to be aware of this type of liver injury but also to report cases. Every doctor should be proactive in reporting cases, so we can better understand which herbal drugs can cause liver injury.

#### Disclosures

*Dr Tagle has no relevant conflicts of interest to disclose.*

#### Suggested Reading

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