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Reducing Drug-Induced Liver Injury

Dr. Buch:

Drug-induced liver injury, or DILI for short, can be caused by a variety of drugs and is a common problem for patients. So how can clinicians help their patients to reduce this injury?

Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch, and today I'm joined by Dr. Jawad Ahmad, who is a Professor of Medicine at Icahn School of Medicine at Mount Sinai in New York. We will be discussing his research on the study of severe liver injury that is caused by prescription medicine and herbal and dietary supplements.

Dr. Ahmad, welcome to the program.

Dr. Ahmad:

Thank you so much. How are you?

Dr. Buch:

Doing great. Let's start with some background, Dr. Ahmad. What testing should be done to confirm a patient has DILI?

Dr. Ahmad:

Well, this is actually quite a difficult area because actually, there is no test to confirm that a patient has DILI. A DILI diagnosis is made by excluding all the other potential causes of liver injury, so typically, things like viral hepatitis, autoimmune hepatitis, and metabolic liver disease. Depending on the clinical situation, maybe there's biliary tract disease, such as gallstones; maybe the patient is hospitalized and has got ischemic hepatitis. So essentially, it's important to run a battery of tests to exclude the other causes of liver disease. And as long as you have a situation where someone's got a liver injury and there's a temporal relationship to having taken a drug or an herbal or dietary supplement, then you can be pretty confident that you've made a diagnosis of DILI.

Dr. Buch:

And diving a little deeper, what are the risk factors more likely to result in DILI?

Dr. Ahmad:

This is a bit more difficult. We used to think that certain factors were important to cause DILI, such as an older patient, sometimes female sex or sometimes patients that are taking lots of different drugs. Those things are probably not so important. The risk factors are probably more genetic, and these are things that we're currently investigating. It's an injury that occurs in someone that's genetically predisposed in some way, and then it also depends on the drug because not all drugs obviously, cause a drug-induced liver injury, and some cause it much more than others. So it depends on the genetic susceptibility as well as the type of drug or herbal and dietary supplement the patient is taking.

Dr. Buch:

Now can you give us some insights into how prescription medicines cause severe liver injury?

Dr. Ahmad:

So this is also an area of investigation and is actually quite difficult. Remember, we're talking about idiosyncratic liver injury here. This is not a predictable liver injury that you get, for instance, with acetaminophen, which basically occurs when you take too much of something, so what we're experiencing is idiosyncratic injury, which means it occurs for no real rhyme or reason. These injuries occur in patients that have some sort of genetic predisposition, and then in the right circumstance are given a drug and it causes sometimes an immune-type injury, sometimes a direct toxic injury. It's sometimes due to a reactive metabolite that's caused. Sometimes it's due to a patient who has a concurrent illness. So there are multiple kinds of converging factors that can lead to an injury, but essentially, it's an injury that's occurring in someone with a genetic predisposition.

Dr. Buch:

And have the genetics been yet defined appropriately?

Dr. Ahmad:

So some of these things have been defined. So we do know the early genetic work has been done on HLA genotypes. Everyone's immune system is a little bit different, and we can kind of classify that based on your HLA haplotype. So certain drugs are associated with liver injury in patients with a certain HLA haplotype. The problem is that this is not the total story. So currently, people are working on, are there other genetic factors that may modify even an HLA haplotype? So this is something that's really in its infancy, and we'll learn more about it in really the coming decades as genetics and also precision medicine improves.

Dr. Buch:

Thank you for that. And what should we know about herbal and dietary supplements causing DILI?

Dr. Ahmad:

So the problem with herbal and dietary supplements is that obviously, these are ubiquitous. Most of the population uses something, and the industry is not really regulated. So no doubt herbal and dietary supplements can cause idiosyncratic liver injury, as can prescription medication. At least with prescription medication, if you know, okay, the person took this particular drug, and we know that this is the compound and this is what was in it. The problem with herbal dietary supplement liver injury is that people are often taking more than one, and the product they are taking may have 20 or 30 different constituents. And the third problem is that sometimes you're not really certain what's in the supplement. So our network investigated this, and basically, the figure is 50 percent, meaning 50 percent of the time what's written on the label of whatever the product is that you're taking is incorrect.

I have a little bit of a soapbox list, I suppose in the sense that the government puts that little label on the bottom of it, saying that, 'this product is not intended to diagnose, treat, or cure any condition,' but it's really never been tested. So I tell patients myself that, "Look, I'm not certain how much you're paying for these things, and I can't argue if you tell me you feel better taking this for whatever reason that you're taking it for, but I can pretty much tell you that it's never been tested, and it probably doesn't work, and you're probably wasting your money, and there is a risk of injury in taking these things."

Dr. Buch:

Thank you very much for that insight. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Jawad Ahmad about drug-induced liver injuries.

Let's turn our attention to diagnosis. How may the RUCAM help with the diagnosis of DILI? And what about the Revised Electronic Causality Assessment Method, or RECAM, that you're working on?

Dr. Ahmad:

So the RUCAM is essentially a scoring system to decide how accurate you think you are when you're making a diagnosis of DILI. So as we talked about earlier, the DILI is a diagnosis of exclusion. So the RUCAM essentially has domains, which assigns a score based on the domain. So for instance, one of the domains is latency. So if you took a drug two years ago, it's very unlikely to cause a liver injury now, so one of the domains is the temporal relationship between when you took the drug and when the injury occurred, and then there's another domain about when you stopped taking the drug; how quickly did the injury improve? You're assigned a score based on the age of the patient and the sex of the patient. You're also assigned a score based on how certain were you in excluding all the other things that we talked about. So did you exclude viral hepatitis, autoimmune disease, or metabolic disease? Did you do imaging? Then also there's a domain about, has this been reported before with this particular product? So essentially, what it is, it's assigning numbers to these domains, and as you chalked up the numbers, the higher the score, the more likely you think that this patient has DILI.

The RECAM is an iteration of the RUCAM where what we've done as a network is try and make it a bit more sophisticated, so we brought in other elements, and it's on an app, and you can download this, and when you have a suspected case of DILI, you can put in the clinical variables and it will essentially give you a score telling you how likely you think this patient has DILI.

Dr. Buch:

Thank you for that. So here are some other tools. How might LiverTox.NIH.gov and DILI Network benefit clinicians?

Dr. Ahmad:

So we'll talk about the DILI Network first. So the DILI Network is several centers throughout the U.S. that are particularly interested in drug-induced liver injury. And essentially, if you have a patient that you think has a drug-induced liver injury and contact one of us, we'll be very happy to talk to the patient and potentially enroll them in our study. So this is really a network where we enroll patients to better understand drug-induced liver injury.

The LiverTox is a fantastic resource to anybody. I have to give a shout-out to Jay Hoofnagle, who is really the driver of this. Essentially, what it has is information about pretty much every prescription drug, over-the-counter drug, and lots of herbal and dietary supplements, and you can search for these. It gives you lots of information about how likely this product will cause liver injury and the type of liver injury that it might cause. It has pathology slides. It has cases that you can read, as well. It also gives you an opportunity to download cases that you might think are drug-induced liver injuries. I must say, I go to the website several times a week even in clinical practice because who can remember a liver injury from doxycycline or something? What kind of injury does it cause? This is something that you could look up very easily on LiverTox, and it will give you the typical injury that it causes, the pathology, and you can see, "Well, does my case look like this case?"

Dr. Buch:

Thank you very much for that. Now moving on to therapies, does N-acetylcysteine have any benefit to treating DILI? And how about steroids?

Dr. Ahmad:

So again, this is a little bit difficult. So one of the problems with drug-induced liver injury is that the type of injury is very variable. So some patients develop hepatocellular injury. Some patients develop kind of a bland cholestasis. Some people develop a vanishing bile duct syndrome. So there's lots of different types of injury. You know, acetylcysteine we use for patients with a Tylenol overdose. We sometimes use them in patients with acute liver failure where we're not certain what the cause is but really, it doesn't have a role in treating DILI. So, if you have a patient that you think has Bactrim-associated DILI, there would be no reason to give acetylcysteine unless you felt the patient has acute liver failure and again, you're not really certain, but there's no real downside, but typically, we would not use that.

Steroids similarly, if a patient has hepatocellular injury and it's behaving a little bit like autoimmune hepatitis. Now sometimes we have the situation where you have a patient that has a liver injury and you're not certain is this autoimmune liver disease? Is this drug-induced liver injury? Or is this maybe drug-induced autoimmune hepatitis? So sometimes when you have that situation, I think it would be not unreasonable to try a steroid, but in DILI just in general, no, there's no role for steroids.

Dr. Buch:

And before we conclude, Dr. Ahmad, are there any other thoughts you would like to share with our audience today?

Dr. Ahmad:

Yeah, there are a few. So DILI, obviously, I see a lot of it. Remember, it's a pretty uncommon event when we're talking about idiosyncratic DILI, so probably one in 10,000 is the figure, but there are some drugs which can cause injury more commonly. Remember also that liver function test monitoring is recommended with multiple drugs actually, so make sure you read the package insert so that you're aware of this. Legal ramifications are possible if you don't. And please, the final thought would be that if you have cases, please reach out to anybody in the DILI Network. And again, the LiverTox is an invaluable resource to everyone.

Dr. Buch:

This has been an excellent review of drug-induced liver injuries, and I'd like to thank my guest, Dr. Jawad Ahmad, for sharing his insights.

Dr. Ahmad, it was a pleasure speaking with you today.

Dr. Ahmad:

Pleasure was all mine.

Dr. Buch:

For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights where you can Be Part of the Knowledge. Thanks for listening, and see you next time.