α-Glutathione S-Transferase: A New Biomarker for Liver Injury?

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Guest:
Dr. William Lee, Professor of Internal Medicine and Bio Engineering at the University of Texas, Southwestern Medical Center at Dallas. Dr. Lee founded the Acute Liver Failure Study Group.

Randye Kaye: Hello and welcome to this edition of "JALM Talk" from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. My name is Randye Kaye and I'll be your host.

For over 60 years, the gold standard tests for evaluation and quantification of liver injury have been serum alanine and aspartate aminotransferase, or ALT and AST. A limitation of these enzymes is that they have relatively long half-lives, so approximately 17 and 47 hours respectively, and therefore do not reflect immediate alterations in liver function. Alpha Glutathione S-transferase is a systolic liver enzyme that has a shorter half-life than ALT and AST and therefore may enable earlier detection of changes in liver injury.

An article entitled "α-Glutathione S-Transferase: A New Biomarker for Liver Injury?" published in the September 2016 issue of JALM, focused on measurement of both ALT and AST and Alpha Glutathione S-transferase in the setting of patients with acute liver failure to determine the utility of this enzyme in detecting alterations in liver function.

The senior author of this article is Dr. William Lee, Professor of Internal Medicine and Bio Engineering at the University of Texas, Southwestern Medical Center at Dallas. Dr. Lee founded the Acute Liver Failure Study Group, a national network to study this organ disease, that has been continuously funded by the NIH since 1997. Dr. Lee is our guest for today's podcast. Welcome, Dr. Lee.

William Lee: Thank you.

Randye Kaye: You're welcome. So tell me, why did you decide to investigate alpha GST at this time?

William Lee: We'd heard about this other enzyme that had a shorter half-life and in some of the literature, it was even as short as an hour, an hour and a half, and we thought it might be a

better measure of what's happening at the hepatocyte level, what's happening inside the liver, if in fact it appears in the circulation more quickly and disappears more quickly once the liver injury is over with.

We went at it by comparing it to the classical enzymes, AST and ALT, that we know have pretty long half-lives and as was mentioned in the introduction, the Acute Liver Failure Study Group has lots of serum samples and lots of clinical data on patients with acute liver failure. The biggest group is the group that comprises almost 50% of the US acute liver failure patients, and that's the group that take acetaminophen in quantities typically exceeding the package labeling and they get a very severe injury, very AST/ALT. So we wanted to compare alpha GST in the acetaminophen patients and look across other forms of liver injury.

Randye Kaye: Okay. So what did you find? What were the main findings?

William Lee: Well, we essentially confirmed the old historical studies. I don't think there was a paper on alpha GST more recently than like 1991 or so. And certainly nobody has done much recently with AST or ALT. I mean, we measure them all the time. It's a standard lab test since the 1950s, but we decided to look at this and compare alpha GST to these other measures using actually a point of care, a really easy assay system, that's just been developed recently.

Now, what we found of course was that alpha GST does in fact have a much shorter half-life. So just to paint the picture again, the acetaminophen patient will have, let's say an AST of -- when he comes in to the hospital sick of let's say, 7,000, so really high. In my lab here, the university laboratory, they just say greater than 7,000 if it's higher than that. But again, acetaminophen patients can even have values as high as 10,000 or 15,000.

At any rate, let's say somebody has an initial value of 5,000. Then with an acetaminophen overdose, the liver injury takes a very short period of time. So the next day, as a clinician, I expect the 5,000 to be down to 3,500, the following day down to maybe 1,800 and the following day down to 600. So very rapid decline over three or four days.

What we found with ALT is it's even slower. So the ALT often peaks the day after the AST peaks, and that's again because ALT has a longer half-life. But alpha GST, the one, the sort of the new kid on the block, if you will, has a very short half-life, so even by the time patient first came into the hospital, we did see one or values that were still rising, but typically the value was already dropping and was normal within 28 hours. And normal often within 24 hours. So very quick decline, again indicating that the half-life was much

shorter. So again, the historical values for AST and ALT were 17 and 47 hours respectively for the half-life.

And again, as I mentioned, the half-life for alpha GST historically had been 60 to 90 minutes. What we found was that the values were about six hours for alpha GST, so a little bit longer than we'd predicted, and 22 hours for AST, and 34 hours for ALT. So again, if you look at them in comparison, the injury was all over probably before the patient came in to the hospital. But only the alpha GST tells you that it's all over with in the next 24 hours by returning to a normal level.

Randye Kaye: So that definitely explains it. The other thing I want to ask you, are there particular settings where the new kid, alpha GST, might be more useful than the transaminases?

William Lee: Sure. I think one that we've been considering is transplant rejections. So in the early period, immediately after putting in a new liver, the enzymes often are very high because there's been an ischemic cold perfusion called preservation injury to the liver. So you often will see AST and ALT elevated for four or five days. But presumably, it's getting better. And again, you could more rapidly see that with alpha GST. So I think alpha GST might help you separate ongoing problems with the new liver from, okay, this is resolved, it's all better, it was reperfusion injury, it's all gone.

And similarly, if you have an episode of acute rejection, the alpha GST is going to go up more quickly than AST and ALT again because it reflects the half-life. Again, once you start your treatment for acute rejection, let's say you give a high dose of corticosteroids intravenously, the alpha GST level will drop within 12 hours. So I think that it would be reassuring to the transplant team to see these responses sort of more real time than sort of, "Oh god! The ALTs are still elevated." Well, the ALT is still elevated because it's got a very long half-life.

Randye Kaye: All right. That makes a lot of sense, so it's sort of quicker and more accurate results. So what are the next steps then, I mean, for example, is the alpha GST available readily to clinicians right now?

William Lee: The company that makes it does have a point of care -- you know, you could put it in your OR, you could put it in -- you could do anywhere. And I imagine it's never made it onto the auto-analyzers, but I mean, I think it could possibly be considered for use in an auto-analyzer setting. The company is named Qualigen and they're out in Carlsbad, California. You know, they just supplied us with the machine. They didn't fund the study.

Randye Kaye: So that answers most of my questions. I just want to ask you, is there anything that you'd like to add to what you've said that you think that people should know.

William Lee: Sure. I think the difference between the acetaminophen or ischemia situations and most other kinds of hepatitis like viral hepatitis, autoimmune hepatitis, other drugs, prescription drugs that cause hepatitis, is that all of that latter group are sub-acute so they come on over several weeks and they just kind of smolder along. I don't think alpha GST would be of particular value there. In fact, in a lot of the cases that we did look because we could compare it, even if there are acute liver failure, they're very bad isoniazid toxicity cases. They still had near normal alpha GST because the half-life is so short that it's cleared as it's produced and it's -- again, if your AST and ALT are only 500, let's say, instead of 5,000, then your alpha GST isn't going to be elevated.

But I mean, this was an insight for us too, that there is a real distinction between ischemia and acetaminophen as the sort of hyper-acute quick onset, quick offset conditions from most other kinds of hepatitis.

Randye Kaye: Okay. Well, thank you so much, very valuable information. And Dr. Lee, thank you for joining us today.

William Lee: Thanks very much. I enjoyed it.

Randye Kaye: That was Dr. William Lee from the University of Texas, Southwestern Medical Center at Dallas, talking about the JALM article, "α-Glutathione S-Transferase: A New Biomarker for Liver Injury?" for this podcast. Thanks for tuning in for "JALM Talk." See you next time and don't forget to submit something for us to talk about.