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Gamma-Glutamyl Transferase in Patients With Primary Biliary Cholangitis

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G&H What are the possible causes for elevations of gamma-glutamyl transferase?

AG Although many factors can cause elevations of gamma-glutamyl transferase (GGT), this enzyme is mainly a marker of liver injury. For example, GGT can be raised because of drug-induced liver injury or liver diseases such as fatty liver disease. In addition, GGT is a marker of cholestasis, such as alkaline phosphatase (ALP), and is frequently increased because of alcohol consumption. Like other liver enzymes, GGT is not specific to only one liver condition, which is why providers typically obtain a panel of liver enzymes and put together different clinical pictures based on biochemical changes.

> ... GGT offers a more dynamic picture of PBC than ALP does because of its faster changes.

G&H What are typical elevations of GGT in patients who have primary biliary cholangitis, and how do these elevations compare with those of ALP?

AG GGT elevations are often seen in patients who have primary biliary cholangitis (PBC). In a recent study that my colleagues and I conducted based on the Global PBC database, most patients had elevated GGT as well as elevated ALP. There were also patients with normal ALP and elevated GGT, and the reverse was also true in that some patients had normal GGT and elevated ALP.

Interestingly, in the very early phases of PBC, many clinicians have noticed elevated GGT before abnormal ALP even though ALP is considered to be the hallmark marker of PBC. Also interesting is that GGT typically falls more rapidly than ALP after the introduction of first-line therapy with ursodeoxycholic acid (UDCA). In other words, GGT offers a more dynamic picture of PBC than ALP does because of its faster changes.

G&H Has research shown that GGT has prognostic value in this patient population?

AG In the aforementioned study, my colleagues and I were the first to show that GGT has prognostic value in patients with PBC. We analyzed data from patients with PBC from the Global PBC database, which consists of 14 institutions, tertiary centers, and liver centers from North America and Europe. We obtained measurements of the patients' serum GGT at baseline and several time points after treatment. We then used statistical models such as the Cox model to evaluate the association between GGT and clinical outcomes (liver transplant and liver-related death). We found that when GGT remained elevated at levels higher than 3.2 times the upper limit of normal after 12

months of first-line treatment with UDCA, prognosis was poor. These patients underwent liver transplant or died more often because of liver complications at 10 years. In our study, GGT was an independent factor for prognosis in PBC even after accounting for known risk factors such as male sex and younger age at diagnosis. Therefore, GGT is a good predictor that can identify patients with PBC who are at higher risk of dying or needing a liver transplant, and essentially offers prognostic information complementary to that offered by ALP. This finding is important because clinicians are told to pay particular attention to ALP in patients with PBC. Our finding suggests that clinicians should also pay attention to GGT in this setting.

G&H What were the other findings and conclusions from this study?

AG Among the more than 2000 patients with PBC in our cohort, the mean age at diagnosis was around 53 years, and more than 90% were female. In tracking GGT for up to 5 years, we noticed that higher serum levels of GGT were associated, in a consistent manner, with a higher probability of dying or undergoing liver transplant.

Our study has implications for patients with PBC who have a high GGT despite having achieved a low level of ALP. An ALP under 1.5 times the upper limit of normal essentially indicates a biochemical response because ALP is the endpoint typically considered in PBC trials. Our study suggests that patients with high GGT should not be ignored. Physicians should look for other disorders, such as cardiometabolic disorders, in these patients; if these disorders can be excluded, treatment escalation should be considered.

We can also conclude that GGT can be used as a primary clinical endpoint for trials. Already some trials in PBC have used GGT instead of ALP, although those trials were planned before our study. Nevertheless, our study provides scientific evidence to support this approach.

G&H What were the limitations of this study?

AG The main limitation was that retrospective data were used instead of prospective data. This was because PBC is a rare condition, so having a large cohort would take decades. Thanks to improvements in medicine, these patients typically do not die very quickly and have a long natural history and disease course. Most of the studies that have been published by the Global PBC study group or the UK PBC study group that are landmark, practice-changing papers have been retrospective in nature owing to the rarity of the condition.

In addition, because of the design of the study, it is not possible to take into account all of the possible confounders, including alcohol and drug exposure. As previously noted, GGT can be elevated in conditions such as fatty liver disease, which is often an issue in liver clinics as well as diabetes clinics and is increasing as the prevalence of obesity increases. Thus, cardiometabolic comorbidities are important potential confounders for elevated GGT. Another limitation of our study is that we were not able to correct for those covariates because they were not present in the Global PBC data set. Nevertheless, regardless of whether the cause is a cardiometabolic condition or an intrinsic liver disease, elevated GGT with normal or near-normal ALP should raise concern for clinicians. If comorbidities such as fatty liver disease and type 2 diabetes are excluded, elevated GGT likely indicates the need for intensified treatment for PBC, as previously noted.

It is important to note that GGT is not a substitute for ALP overall; GGT is generally complementary and adds value.

G&H How strong is the correlation between GGT and ALP in patients with PBC? Can GGT ever replace ALP in this setting?

AG The correlation was strong in our study, with an *r* value of 0.71, which is remarkable. Because ALP is considered to be the hallmark marker of PBC, this correlation shows that GGT has value as well. However, the *r* value was not 1, indicating that GGT and ALP are not the same marker.

It is important to note that GGT is not a substitute for ALP overall; GGT is generally complementary and adds value. ALP is an excellent biomarker. Nevertheless, there are a few situations where GGT can safely replace ALP, for example, when there is doubt about a differential diagnosis related to osteoporosis or bone disorders, such as in postmenopausal women. ALP can be less specific in this setting, as it can be elevated owing to bone disease, and patients with PBC are often postmenopausal women. Thus, GGT has particular value in a patient with PBC and osteoporosis. If the patient's GGT and ALP are elevated despite treatment, the provider should intensify treatment for PBC by considering add-on therapies with the aim of

reducing GGT together with ALP. On the other hand, if the patient's GGT is normal, an elevated ALP does not necessarily reflect a bile duct or liver issue.

G&H Should GGT be used for screening or monitoring patients with PBC?

AG There is wide variety in the use of GGT in patients with PBC around the world. In some countries, GGT is required for monitoring, together with ALP and transaminases. Other countries use either GGT or ALP; they do not use both markers. There is currently no consensus on this issue. Our study offers scientific evidence to support the role of GGT in the monitoring and follow-up of patients with PBC. I and other Global PBC study investigators endorse the use of GGT with validated risk scores that include bilirubin and ALP.

G&H How can GGT be used as a clinical trial endpoint in this setting?

AG Our study showed the prognostic role of GGT. We cannot offer a clear threshold for investigators to use GGT as a primary efficacy outcome. However, many plots in our work showed that the lower the GGT, the better the outcome. We also showed that reducing GGT to a value equal to or greater than 66% from baseline resulted in better liver transplant survival. This could be helpful to investigators if they need to plan what percentage of GGT decrease is meaningful in a clinical trial.

G&H What research is still needed regarding GGT in patients with PBC?

AG The next steps are to better investigate the influence of body mass index, alcohol consumption, and all other possible confounders of GGT in patients with PBC. Population-based registries such as the UK-PBC or the Italian PBC Registry represent a valuable tool for further research projects on GGT in patients with PBC. These registries have the potential to capture cases outside tertiary centers, reducing selection bias. Another important research topic that needs attention in the near future is the role of GGT as a predictive response marker to second- and third-line therapies for PBC.

Disclosures

Dr Gerussi consults for Ipsen and has received speaker's fees from Advanz Pharma.

Suggested Reading

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