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Spontaneous fluctuations in liver biochemistries in patients with compensated NASH cirrhosis: Implications for drug hepatotoxicity monitoring

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Abstract

Background: Patients with cirrhosis may have spontaneous fluctuations in liver enzymes, which may confound detection of drug-induced liver injury (DILI), but these fluctuations have not been described.

Objective: We sought to quantify spontaneous liver enzyme abnormalities in patients with cirrhosis due to nonalcoholic steatohepatitis (NASH) enrolled in clinical trials.

Methods: We examined the laboratory values of patients with compensated cirrhosis randomized to placebo in two clinical trials for NASH. Patients in one study were followed every 13 weeks up to week 57, and in the other study, patients were followed every 4 weeks up to week 120.

Results: 53 and 85 patients were randomized to placebo in the trials. Baseline alanine aminotransferase (ALT) was > laboratory upper limit of normal (ULN) in 53% and 49% of participants, AST was >ULN in 49% and 59%, alkaline phosphatase was >ULN in 36% and 27%, and bilirubin was >ULN in 13% and 19%. During follow-up, ALT increased to 2x baseline in 8% and 15%, AST increased to 2x baseline in 6% and 21%, and bilirubin increased to 2x baseline in 9% and 18%. Alkaline phosphatase did not increase to 2x baseline for any patient. The maximum ALT was 3x ULN in 9% and 12%. ALT increased to 3x baseline in three patients and to 5x ULN

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Research involving human participants: Both studies were approved by the appropriate institutional review boards and were conducted in compliance with regulatory requirements.

Informed consent: Informed consent was obtained from all individual participants included in the studies.

in two patients. No patients had elevations consistent with Hy's law. Maximum ALT for patients with abnormal baseline was higher (median 48 [range: 34 – 299] U/L) and (56 [47 – 85] U/L) than that for those with normal baseline (26.5 [18 – 33] U/L) and (29 [25.5 – 30.5] U/L) in both studies respectively with a p-values < 0.001.

Conclusion: Spontaneous liver enzyme abnormalities are common in patients with NASH cirrhosis in clinical trials, and these abnormalities can rarely meet criteria for DILI suspicion. Further work to better define these abnormalities and continued vigilance to detect DILI in this population is needed.

1. INTRODUCTION

Drug-induced liver injury (DILI) is a rare complication of prescription medications in the general population, affecting up to 19 per 100,000 people [1]. For those affected, the consequences can be dire; DILI is a leading cause of acute liver failure, and liver failure due to DILI is associated with high mortality [2, 3]. DILI is therefore a common reason for halting of drug development and for drug withdrawal from the market [4]. DILI is characterized as being intrinsic or idiosyncratic based on its pathogenesis. Intrinsic DILI is predictable, dose-dependent, and typically detected in early phases of drug development. Conversely, idiosyncratic DILI is unpredictable, and is therefore detected in later phases of drug development such as clinical trials and post-marketing surveillance [5]. This latter type of DILI remains an area of intense concern in clinical trials. Poor DILI outcomes have been associated with several risk factors, and in particular increased mortality has been seen in those with pre-existing chronic liver disease [6].

Despite the increased risk for poor outcomes in this population, chronic liver disease is an important target for new drug development. The increasing prevalence of nonalcoholic steatohepatitis (NASH) coupled with an improved understanding of its pathogenesis has created demand for the development of new NASH therapeutics, and numerous agents are in various stages of development [7–11]. There has also been increasing investigation into therapeutics for patients with more advanced chronic liver disease (e.g. cirrhosis, portal hypertension) [12, 13]. In these populations, investigators must be vigilant in detecting idiosyncratic DILI to prevent poor outcomes, but they must also take into account the spontaneous liver enzyme abnormalities and fluctuations that occur in patients with chronic liver disease. In effect, we must be able to distinguish the signal from the noise. Although spontaneous changes in liver enzymes have been examined in clinical trials, these trials have largely excluded patients with known liver disease [14, 15]. Additional studies examining liver enzyme biological variability have also predominantly examined populations without liver disease [16]. Therefore, there remains a gap in the literature concerning spontaneous liver enzyme abnormalities in patients with cirrhosis participating in clinical trials.

To address this gap, we examined data from two randomized clinical trials studying the liver histologic and portal hemodynamic response to investigational agents in patients with compensated NASH cirrhosis. The underlying question is whether spontaneous fluctuations in liver enzymes might resemble idiosyncratic DILI in this population, and thus complicate DILI detection in clinical trials. In order to quantify spontaneous fluctuations in liver

enzymes that were not due to study drug, we specifically reviewed patients in the placebo arms of these trials. Absolute values of liver enzymes as well as values relative to the upper limit of normal were recorded at baseline and during follow-up.

2. METHODS

2.1. Clinical Trials

Study GT 026 (GT;) is a phase 2, North American, multicenter randomized trial that examined the safety and efficacy of GR-MD-02 (belapectin), a galectin-3 inhibitor, in 162 patients with NASH cirrhosis and portal hypertension [17]. Participants were followed for one year, with study visits including standard laboratory assessments every 13 weeks. The primary outcome measure was the change in hepatic venous pressure gradient (HVPG) at the end of the study compared to baseline. Study GS-US-321–0106 (GS;) is a phase 2b randomized trial examining the safety and efficacy of simtuzumab, a monoclonal antibody against lysyl oxidase-like 2, in 258 patients with compensated NASH cirrhosis, also with a primary efficacy outcome of change in HVPG [13]. The study was halted after 96 weeks (out of a planned 240 weeks) due to a preplanned analysis showing a lack of efficacy, and during the study, participants received standard laboratory assessments every 4 weeks. In both studies, patients were randomized 1:1:1 to receive either one of two doses of investigational agent, or placebo. Both studies were approved by the appropriate institutional review boards and were conducted in compliance with regulatory requirements. Informed consent was obtained from all individual participants included in the studies.

2.2. Participants

Participants in both trials were required to have a liver biopsy consistent with NASH cirrhosis and exclusion of other causes of chronic liver disease. They also were required to have both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤10x the upper limit of normal (ULN). Patients with any symptoms suggestive of decompensated cirrhosis (ascites, hepatic encephalopathy, or variceal bleeding) were excluded, as were patients with hepatocellular carcinoma. Allowed ages in GT were 18–75; in GS, allowed ages were 18–65. In the GT trial, for inclusion, patients were required to have portal hypertension (HVPG ≥6 mmHg), and patients were excluded if they had medium/large varices or varices with red signs; neither of these eligibility criteria were required for the GS trial. GT also excluded participants with a model for end stage liver disease (MELD) score ≥15 or Child Turcotte Pugh Class B or C. GS excluded participants with alcohol consumption greater than 21 oz/week for males or 14 oz/week for females. These discrepancies in eligibility criteria resulted in fundamental differences between the two study samples. Complete study eligibility criteria are reported elsewhere [13, 17]. Per the study protocols, study drug was interrupted for ALT >5x ULN for those with normal baseline ALT (or 5x baseline for those with elevated baseline) or for a bilirubin increase of 2 mg/dL for those with a normal baseline (or a doubling of direct bilirubin for those with Gilbert’s syndrome). For patients with liver-related symptoms, the ALT thresholds were 3x ULN or baseline. Further stopping rules included elevated bilirubin with symptoms of hypersensitivity. None of the patients met these pre-specified criteria for study drug interruption.

Because our interest was the spontaneous fluctuation in liver enzymes in patients with NASH cirrhosis (not due to study drug), we included only those patients in both studies who were randomized to receive placebo. One patient had identical laboratory values throughout all study visits; this patient was excluded. To avoid biased estimates due to loss to follow-up, we did not include study visits with data from fewer than 50% of participants (up to week 57 in GT; week 120 in GS).

2.3. Variables

The primary variables of interest were serum liver enzymes (AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin) at baseline and during follow-up visits. Additional variables included baseline age, sex, body mass index, HVPG, diabetes, and laboratories to calculate a MELD score [18].

2.4. Statistical Analysis

The two studies were examined separately due to differences in inclusion/exclusion criteria and follow-up protocols. Continuous variables were described using means and standard deviations (SD), or medians and ranges for non-normally distributed variables and compared with the Wilcoxon-Rank sum test. Categorical variables were described using counts and proportions. Because of the importance of laboratory ULN in the assessment of drug safety and DILI, liver enzymes were additionally specified based on the proportion above different multiples of the ULN. The ULN for the studies were based on the central laboratory reference ranges determined by the laboratory. The ULN for ALT was 33 U/L in women and 40 U/L in men; for AST the ULN was 36 U/L in women and 43 U/L in men. For men and post-menopausal women, the ULN for alkaline phosphatase was 115 U/L, and for women aged <51 years, the ULN was 90 U/L. The ULN for total bilirubin was 1.1 mg/dL for both sexes, and the ULN for direct bilirubin was 0.4 mg/dL. Maximum values of liver enzymes during follow-up were determined, and these were used to assess the maximum increase from baseline. We plotted peak ALT and total bilirubin using the methodology of the evaluation of Drug-Induced Serious Hepatotoxicity (eDISH), a graphical tool that is used by the US Food and Drug Administration to assess drug safety [19]. In eDISH, peak ALT is plotted on the x-axis, and peak total bilirubin is plotted on the y-axis as multiples of the ULN in log scale. We assessed the proportion of participants who met criteria for Hy's law (hepatocellular injury with AST or ALT >3x ULN and total bilirubin >2x ULN without cholestasis [alkaline phosphatase <2x ULN]) [20]. Hy's law is a commonly-used metric associated with poor prognosis for patients with DILI [21]. Potential Hy's law cases can be identified in the right upper quadrant of the eDISH plot. The right lower quadrant of eDISH is denoted Temple's Corollary, which is a non-specific indicator of potential DILI. The left upper quadrant is the cholestasis quadrant, which can be seen with cholestatic liver injury. All analyses were performed using SAS version 9.4 (Cary, NC).

3. RESULTS

3.1. Participant Characteristics

In the GT and GS trials, 53 and 85 patients were randomized to placebo, respectively. Baseline characteristics are shown in Table 1. In both studies, the majority of patients were

female, and most had diabetes. The mean body mass index was approximately 35 kg/m^2. Patients in GT were older, had a greater proportion of women, fewer with diabetes, and slightly higher mean MELD score.

3.2. Baseline Liver Enzymes

Approximately 50% of participants in both studies had ALT >ULN; 4 participants in GT and 1 in GS had ALT >3x ULN (Table 2). Elevated baseline AST was present in 49% of patients in GT and in 59% of GS patients. Baseline AST was greater than ALT in 64% of GT patients and in 70% of GS patients. Elevated baseline alkaline phosphatase was less common; it was >ULN in 36% of patients in GT and in 27% of those in GS. None had alkaline phosphatase >3x ULN in either study. Similarly, total bilirubin was elevated in 13% of patients in GT and in 19% of GS patients, and none were >3x ULN. Direct bilirubin was elevated in 14% of GT patients and in 8% of GS patients.

3.3. Overview of Liver Enzymes During Follow-up

3.3.1. GT Study—During follow-up, most patients had at least one liver enzyme value greater than baseline across all four liver enzymes (Table 3). The median of the maximum increase in ALT above baseline was 10 U/L (range 1–90). This increase was at least 1.5x baseline in 19% of patients, but only 4% had an increase >3x baseline. The maximum value of ALT ranged from 18 to 299 U/L, and 75% of participants had ALT >ULN. The maximum ALT was >3x ULN in 9%. The distribution of follow-up ALT in GT is shown in Figure 1. The increase in AST over baseline was similar to ALT, with 30% having an increase >1.5x baseline and 2% having an increase >3x baseline (Table 3). The absolute maximum AST ranged from 30 to 177 U/L. The maximum AST was >3x ULN in 8%. The maximum AST was greater than maximum ALT in 62% of patients. Although 77% of patients had an increase in the alkaline phosphatase over baseline, none increased by 1.5x baseline (maximum increase 60 U/L). The maximum alkaline phosphatase was >ULN in 51%, and none had a maximum >3x ULN. The maximum increase in total bilirubin was 0.3 mg/dL (range 0.0–1.2); the total bilirubin increased by 2x baseline in 9% (only 4% increased the indirect bilirubin by 2x baseline). All patients had at least one total bilirubin >ULN during follow-up, but only 21% had direct bilirubin >ULN. Three patients (6%) had a total bilirubin >2x ULN (two had direct bilirubin >2x ULN); none had a total or direct bilirubin >3x ULN. The eDISH plot displaying peak ALT and total bilirubin is shown in Figure 2. Three of the patients (5.7%) had peak values in the cholestasis quadrant, and three other patients met Temple's Corollary, but no participants met criteria for Hy's law at any point. The distributions of follow-up AST, alkaline phosphatase, and bilirubin are shown in the Supplementary Figures. Shift tables and plots demonstrating the maximum AST and ALT as a function of baseline liver enzymes are also shown in the Supplementary Figures and Table. Patients with normal baseline ALT had a significantly lower maximum ALT (median 26.5 [range: 18 – 33] U/L) than those with abnormal baseline (48 [34 – 299] U/L; $p < 0.001$).

3.3.2. GS Study—There were increases in each liver enzyme over baseline in >90% of participants in GS (Table 3). ALT increased to >1.5x baseline in 39% of patients, but only one patient increased to >3x baseline. The maximum ALT ranged from 24 to 276 U/L, and 78% had maximum ALT >ULN. ALT increased to >3x ULN in 12%. Follow-up ALT in GS

is shown in Figure 3. GS participants had greater increases in AST as compared to GT (Table 3): AST increased over baseline in 89%, including an increase of >1.5x baseline in 48% and >3x baseline in 4%. The maximum AST ranged from 20 to 250 U/L, and 93% had a follow-up AST >ULN. 12% had AST >3x ULN. Maximum AST was greater than maximum ALT in 72%. Alkaline phosphatase increased over baseline in 96% of participants, and the increase was >1.5x baseline in 16%. The maximum alkaline phosphatase ranged from 37 to 370 ULN. It was >ULN in 52%, with one patient having a maximum alkaline phosphatase >3x ULN. The total bilirubin increased by 1.5x baseline in 48% and by 2x baseline in 18%, to a maximum ranging from 0.4 to 6.3 mg/dL (0.1 to 2.6 mg/dL direct bilirubin). The maximum total bilirubin was >2x ULN in 13% (direct bilirubin >2x ULN in 9%). Several patients had a total bilirubin >4 mg/dL. However, corresponding direct bilirubin values were substantially lower; the maximum direct bilirubin was 2.6 mg/dL and most had direct bilirubin <2 mg/dL. Further, those with elevated bilirubin during follow-up had abnormal bilirubin at baseline. Thus, study drug did not have to be withheld. The eDISH plot for the GS study is shown in Figure 4. There were no patients that met Hy's law criteria; 11 patients (12.9%) had peak values in the cholestasis quadrant, and 10 (11.8%) met criteria for Temple's Corollary. Notably two patients in the Temple's Corollary quadrant had abnormally high total bilirubin levels that very nearly met Hy's law criteria, but remained lower than the strict 2x ULN definition. Follow-up laboratory distributions are shown in the Supplementary Figures. Maximum AST and ALT stratified according to the baseline values are also shown in the Supplementary Figures and Table. Patients with normal baseline ALT had a significantly lower maximum ALT (median 29 [range: 25.5 – 30.5] U/L) than those with abnormal baseline (56 [47 – 85] U/L; $p < 0.001$).

4. DISCUSSION

In this detailed follow-up of patients with compensated NASH cirrhosis receiving placebo in two clinical trials, abnormal liver enzymes were common, with approximately half of patients having elevated ALT at baseline and three-fourths having elevated ALT at any point during follow-up. Additionally, these abnormalities were substantial; approximately 10% had at least one ALT >3x ULN, and 20–40% had an increase in the ALT of 1.5x baseline. These novel findings are in stark contrast to other studies of non-cirrhotic patients. For example, in over 4,200 participants with heart disease randomized to placebo for 36 months, only 5 ALT values were >3x ULN [14]. Likewise, in nearly 600 participants with type 2 diabetes randomized to placebo in 13 clinical trials, only 5% had elevated baseline ALT and <1% developed ALT >3x ULN [15].

These findings highlight the challenge of detection and confirmation of idiosyncratic DILI in clinical trials for NASH and advanced liver disease. This challenge in detecting DILI has long been recognized in trials for non-cirrhotic NASH, where natural fluctuations in aminotransferases may also confound DILI detection [8, 22]. Traditional guidance has relied on thresholds based on multiples of the ULN to trigger concern for DILI (ranging from 3x to 5x ULN) [20, 23]. Notably, several patients in this study met criteria for DILI concern based on Temple's Corollary. However, for patients with baseline elevations, simply using multiples of the ULN may be inappropriate to signal potential DILI. Recent consensus guidelines for detecting DILI in non-cirrhotic NASH trials have instead advocated a hybrid

approach [24, 25]. For those with normal baseline ALT, they propose a threshold based on the ULN; for those with elevated baseline ALT, they propose a threshold based on the increase over baseline. Whether these thresholds can be applied to trials for NASH cirrhosis remains unclear; however, our findings may support similar thresholds in this population. Several patients met criteria for DILI concern based on standard FDA guidance (Temple's Corollary). However, none met the hybrid criteria which vary depending on the baseline enzyme levels: the three patients who developed ALT >3x baseline had baselines below the ULN and did not reach the required >5x ULN; the two patients who developed ALT >5x ULN had elevated baseline and did not reach >3x baseline. Further standardization of DILI concern criteria may help with adjudication in this population.

Further complicating the detection of idiosyncratic DILI in patients with NASH cirrhosis is the increased potential for poor outcomes in those affected. Although patients with chronic liver disease do not appear to be at increased risk for DILI compared to patients without liver disease, they experience more severe liver injury and are at greater risk for death [6]. The stakes are therefore higher in this population, and the accurate early identification of DILI takes on greater importance. The identification of poor prognosis associated with DILI relies on Hy's law, and it remains unclear whether patients with impaired liver function and fluctuating liver enzymes could develop a signal resembling Hy's law spontaneously [20]. Such a signal could confuse investigators, who might mistake severe DILI for NASH cirrhosis-related liver enzyme fluctuation. In this respect our data are reassuring; none of the patients in either trial fulfilled criteria for Hy's law (although two patients in the GS study very nearly met those criteria). The presence of labs meeting criteria for Hy's law remains an ominous sign in any population, and should not be dismissed as the spontaneous fluctuations of liver enzymes in patients with NASH cirrhosis.

DILI is a diagnosis of exclusion, but even after excluding alternative causes of abnormal liver enzymes, establishing DILI causality remains difficult [26]. Establishing causality entails conducting a thorough diagnostic work-up, maintaining close follow-up, and potentially re-challenging with the suspected agent when necessary [27, 28]. Liver enzymes can play a helpful role in establishing causality when they normalize upon withdrawal of the suspected medication. Our results demonstrate that liver enzymes in NASH cirrhosis can fluctuate unpredictably in the absence of ongoing DILI, which diminishes their usefulness in the assessment of causality.

An additional challenge in diagnosing DILI in patients with cirrhosis concerns the presence or absence of symptoms. Investigators may use the onset of non-specific symptoms during a trial (e.g. fatigue, nausea, vomiting, right upper quadrant pain) to raise DILI suspicion and expedite liver enzyme evaluation [20, 29]. Indeed, when such symptoms occur, consensus guidelines recommend the use of lower ALT thresholds to detect and manage suspected DILI [24]. However, patients with NASH, and particularly those with cirrhosis, commonly have multiple of these same symptoms in association with their underlying disease that could be confused with symptoms of DILI [30]. In this study, we did not have data on the emergence or fluctuation of symptoms during follow-up. It remains unclear how to use patient-reported symptoms in this context, although given the seriousness and potential severity of DILI in this population, a conservative approach may be prudent.

In addition to lacking data on patient symptoms, this study has several other limitations such as a lack of information on some potential confounding factors. For example, concomitant medications could theoretically cause some of the observed liver enzyme fluctuations; however, such confounding is unlikely given the rarity of DILI. Other confounding causes for abnormal liver enzymes are also unlikely, as patients with other liver diseases or ongoing alcohol consumption were excluded from the studies, and there were no liver-related adverse events reported in the trials. Although the study sample sizes were adequate and powered for the trial outcomes, examining only the placebo arms resulted in a relatively small sample size, particularly since both trials had two active treatment arms compared to only one placebo arm. Limited data on the active arms did not allow us to examine DILI due to the study agents, but our focus in this analysis was primarily on background fluctuations not due to study drugs. Additionally, the strict study eligibility criteria led to sample homogeneity, which precluded subgroup analyses, such as examination of patients with decompensated cirrhosis, who were excluded from the studies. These criteria limit the generalizability of the findings. However, similar criteria are likely to be used in future clinical trials in this population; thus, the findings are likely to be applicable to future trials as well. In contrast, the study benefits from the detailed study protocols that required close follow-up of patients with very frequent laboratory testing. This frequent liver enzyme assessment is unlikely to be achieved outside of a clinical trial protocol.

In conclusion, abnormal liver enzymes in patients with NASH cirrhosis receiving placebo in two clinical trials were common, but they rarely exceeded standard thresholds for DILI suspicion. As additional studies are performed in this population, it will be important to remain vigilant to the appearance of potential DILI, but specific challenges remain, particularly with regard to baseline laboratory test fluctuations. Further work in larger samples is needed to better define these baseline fluctuations and to help guide future recommendations for DILI detection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

- Spontaneous fluctuations in liver enzymes are common in patients with NASH cirrhosis receiving placebo in clinical trials.
- The spontaneous liver enzyme fluctuations that occur in patients with NASH cirrhosis can rarely meet criteria for DILI suspicion.

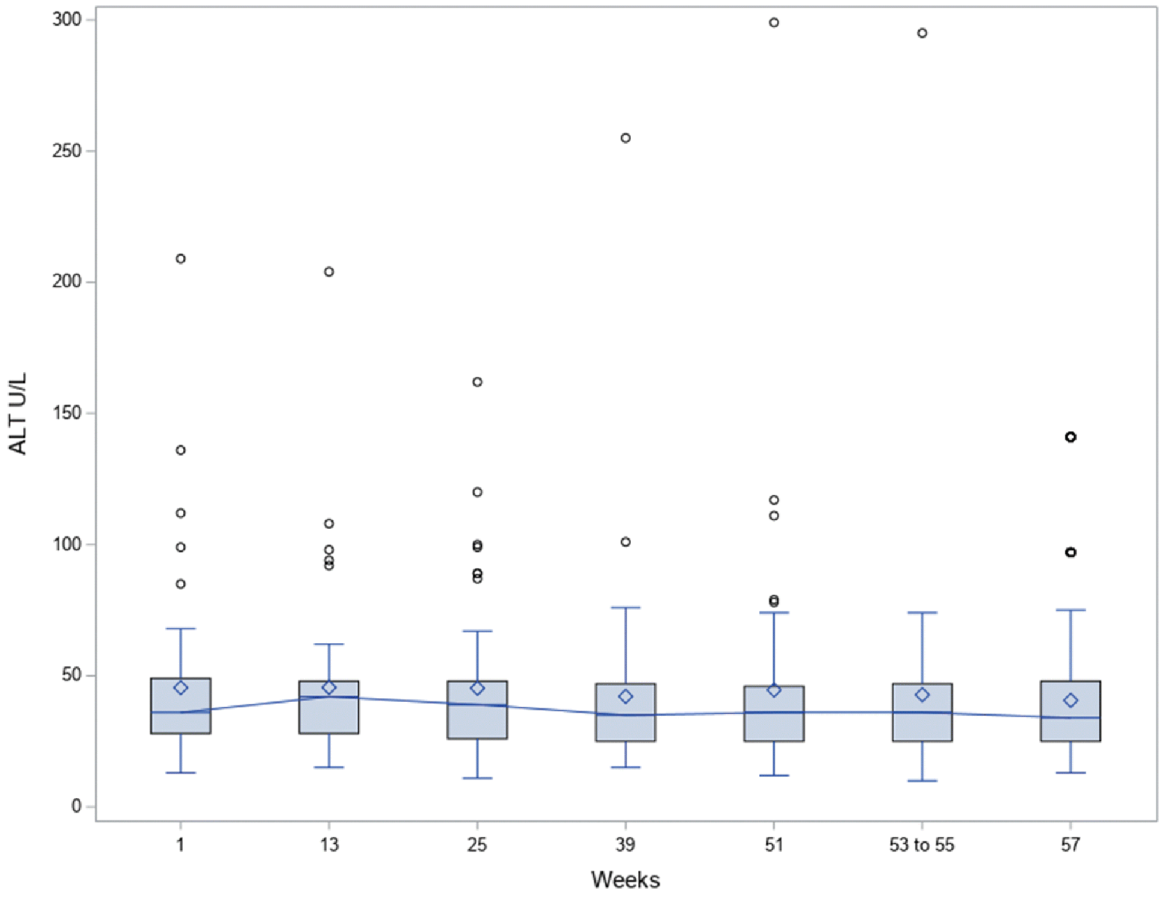

Figure 1.
Distribution of ALT during baseline and follow-up in the GT study. The frequency of elevated ALT was common throughout the study follow-up.

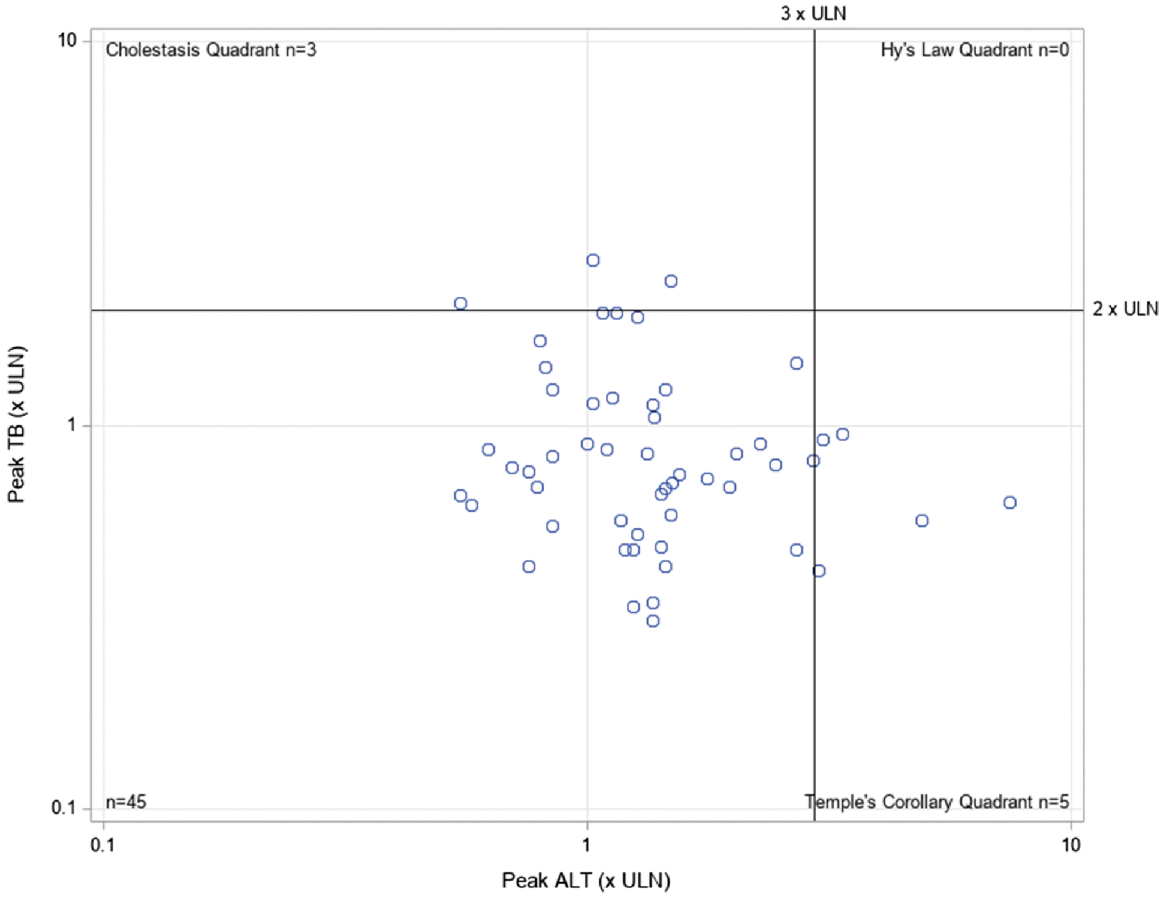

Figure 2.

eDISH plot of peak ALT and peak total bilirubin in the GT study. No patients fulfilled criteria for Hy's law, but several fulfilled Temple's Corollary.

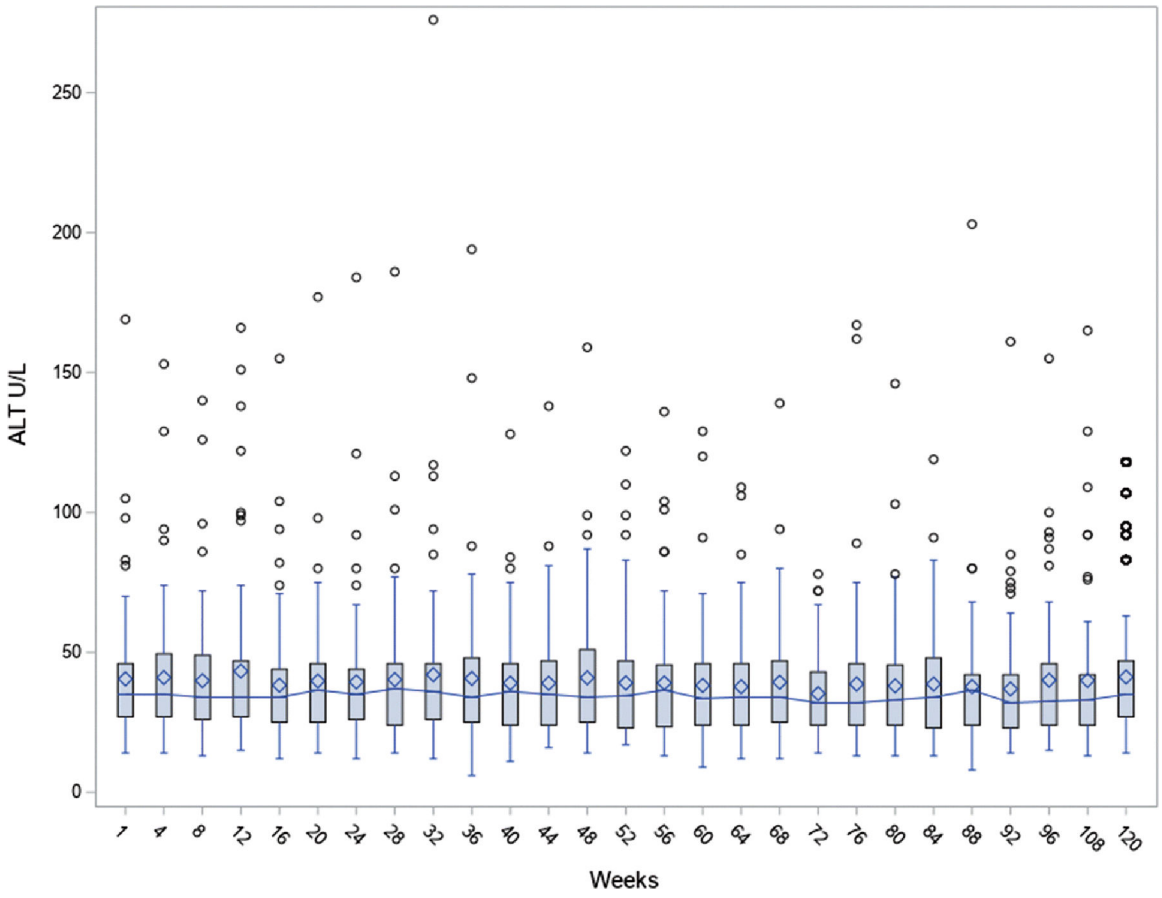

Figure 3.
Distribution of ALT during baseline and follow-up in the GS study. The frequency of elevated ALT was common throughout the study follow-up.

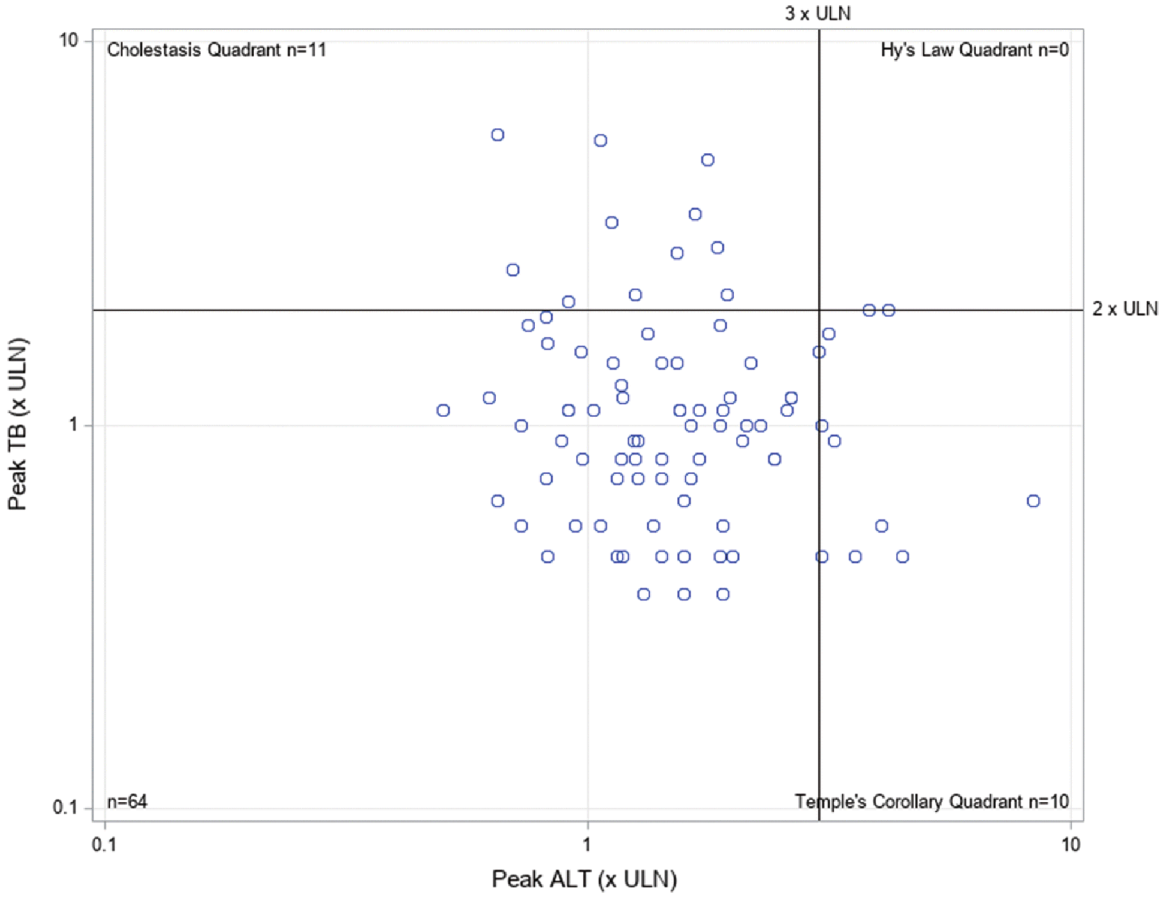

Figure 4.

eDISH plot of peak ALT and peak total bilirubin in the GS study. No patients fulfilled criteria for Hy's law, but several fulfilled Temple's Corollary.

Table 1.

Patient Characteristics

	GT (N=53)	GS (N=85)
Age, mean (SD)	58 (8.6)	56 (7.8)
Female, n (%)	37 (70)	56 (66)
BMI, mean (SD)	35 (7.3)	34.7 (7.7)
HVPG, mean (SD)	12 (4.0)	13 (5.3)
Diabetes, n (%)	32 (60)	60 (71)
Creatinine, mean (SD)	0.7 (0.2)	0.8 (0.2)
MELD, mean (SD)	7.5 (2.0)	6.6 (0.5)

BMI: Body Mass Index

HVPG: Hepatic Venous Pressure Gradient

MELD: Model for End-stage Liver Disease

Table 2.

Baseline Liver Tests

	ALT		AST		ALP		Total Bilirubin		Direct Bilirubin	
	GT	GS	GT	GS	GT	GS	GT	GS	GT	GS
Baseline, median (range)	36 (13–209)	35 (14–169)	40 (22–115)	42 (16–129)	100 (55–218)	90 (32–287)	0.6 (0.2–2.4)	0.6 (0.2–4.8)	0.3 (0.2–0.7)	0.2 (0.1–1.3)
> ULN, n (%)	28 (53)	42 (49)	26 (49)	50 (59)	19 (36)	23 (27)	7 (13)	16 (19)	4 (14)	7 (8)
>1.5x ULN, n (%)	11 (21)	16 (19)	10 (19)	17 (20)	2 (4)	6 (7)	3 (6)	7 (8)	1 (4)	5 (6)
>2x ULN, n (%)	6 (13)	7 (8)	5 (9)	10 (12)	0 (0)	3 (4)	2 (4)	4 (5)	0 (0)	2 (2)
>3x ULN, n (%)	4 (7)	1 (1)	1 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
>5x ULN, n (%)	1 (2)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

ULN: Upper Limit of Normal

ALT ULN: Women 33 U/L and Men 40 U/L

AST ULN: Women 36 U/L and Men 43 U/L

ALP ULN: Post-menopausal Women and Men 115 U/L and Women < 51 years old 90 U/L

Total Bilirubin ULN: 1.1 mg/dl for Both Sexes

Direct Bilirubin ULN: 0.4 mg/dl for Both Sexes

Table 3.

Liver Tests During Follow-up

	ALT		AST		ALP		Total Bilirubin		Direct Bilirubin	
	GT	GS	GT	GS	GT	GS	GT	GS	GT	GS
Increase over baseline, n (%)	37 (70)	79 (93)	41 (77)	76 (89)	41 (77)	82 (96)	44 (83)	79 (93)	19 (68)	75 (88)
Maximum increase over baseline, median (range)*	10 (1–90)	16 (1–107)	14 (1–95)	21 (2–134)	15 (1–60)	21 (1–125)	0.3 (0.0–1.2)	0.4 (0.1–4.0)	0.1 (0.0–0.5)	0.1 (0.0–1.9)
Maximum increase over baseline, n (%)										
> 1.5x baseline	10 (19)	33 (39)	16 (30)	41 (48)	0 (0)	14 (16)	23 (43)	44 (48)	7 (13)	41 (48)
> 2x baseline	4 (8)	13 (15)	3 (6)	18 (21)	0 (0)	0 (0)	5 (9)	15 (18)	2 (4)	17 (20)
> 3x baseline	2 (4)	1 (1)	1 (2)	3 (4)	0 (0)	0 (0)	0 (0)	4 (5)	0 (0)	7 (8)
Maximum, median (range)	47 (18–299)	51 (24–276)	49 (30–177)	64 (20–250)	117 (59–249)	111 (37–370)	0.87 (0.3–3.0)	1.1 (0.4–6.3)	0.3 (0.2–0.9)	0.3 (0.1–2.6)
Maximum value, n (%)										
> ULN	40 (75)	66 (78)	40 (75)	79 (93)	27 (51)	44 (52)	53 (100)	85 (100)	11 (21)	23 (27)
> 1.5x ULN	18 (40)	43 (51)	21 (40)	54 (64)	6 (11)	15 (28)	7 (13)	21 (25)	3 (6)	9 (11)
> 2x ULN	11 (21)	21 (25)	12 (23)	29 (34)	2 (4)	5 (6)	3 (6)	11 (13)	2 (4)	8 (9)
> 3x ULN	5 (9)	10 (12)	5 (8)	9 (12)	0 (0)	1 (2)	0 (0)	5 (6)	0 (0)	4 (5)
> 4x ULN	2 (4)	4 (5)	2 (4)	2 (2)	0 (0)	0 (0)	0 (0)	3 (4)	0 (0)	2 (2)
> 5x ULN	1 (2)	1 (1)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	1 (1)

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Total Bilirubin ULN: 1.1 mg/dl for Both Sexes

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