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ORIGINAL ARTICLE

Rise in alanine aminotransferase after HCV treatment is a highly sensitive screen for treatment failure

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Abstract

Nucleic acid testing to confirm sustained virological response (SVR) after HCV therapy is technical, often expensive, and frequently unavailable where disease prevalence is highest. Alternative surrogate biomarkers merit evaluation. In a short-treatment trial in Vietnam (SEARCH-1; n = 52) we analysed how changes in alanine transaminase (ΔALT) and aspartate transaminase (ΔAST), from end of treatment (EOT) to EOT + 12 weeks, related to SVR, defined as HCV RNA < lower limit of quantification 12 weeks after EOT. In a separate UK trial (STOPHCV1; n = 202), we then tested the hypothesis that any elevation in ALT or AST between EOT and EOT12 is a sensitive screen for treatment failure. In SEARCH-1, among 48 individuals with data, 13 failed to achieve SVR. Median ΔALT and ΔAST were negative in cured patients but elevated when treatment failed [median ΔALT (IQR): −2 IU/L (−6, +2)] versus +17 IU/L (+7.5, +38) ($p < 0.001$). Amongst treatment failures, 12/13 had increase in ALT and 13/13 had increase in AST after EOT, compared with 12/35 in those cured. In STOPHCV1, 196/202 patients had evaluable data, of which 57 did not achieve SVR. A rise in ALT after EOT was 100% sensitive (95% C.I. [93.7 – 100%]) and 51% specific (42.4 – 59.7%) for detecting treatment failure. ΔAST > 0 IU/L was 98.1% (89.9 – 99.9%) sensitive and 35.8% (27.3 – 45.1%) specific. A rise in ALT or AST after HCV therapy is a highly sensitive screen for treatment failure in mild liver disease. This finding could reduce costs and complexity of managing HCV.

Abbreviations: ALT, Alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral; EOT, end of treatment; IQR, interquartile range; NAT, nucleic acid testing; SVR, sustained virological response.

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INTRODUCTION

WHO has called for a simplification of HCV care to improve access to treatment.[1] Pan-genotypic direct-acting antivirals (DAAs) achieve cure rates of >95%, with cure defined by sustained virological response (SVR) on nucleic acid testing (NAT) 12–24 weeks after end of treatment (EOT). However, NAT is often expensive, particularly in resource-limited settings, which shoulder the highest burdens of disease. In Vietnam, public sector NAT is priced at US$37–$90[2] per test and is not government subsidized. NAT also involves technical expertise, requiring the samples to be transported to specialized laboratories or tested with novel point-of-care platforms, which are frequently unavailable. This impedes decentralization of care. Alternative surrogate biomarkers merit evaluation.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are nonspecific markers of liver inflammation that are routinely tested before and after HCV treatment. Elevated pretreatment ALT levels have been associated with slower virological response,[3] and pretreatment levels of both enzymes have been associated with failure to achieve SVR,[4] though neither are reliably predictive. Both enzymes decline on therapy,[5–7] and in the pre-DAA era, a "sustained biochemical response" was used as a surrogate for SVR.[6,7] Elevated ALT levels (greater than upper limit of normal) at EOT and EOT + 12 weeks have also been associated with DAA treatment failure,[8,9] but we found no published data evaluating how changes in ALT and AST after EOT relate to DAA outcomes or their sensitivity for detecting treatment failure.

Experimental treatment-shortening trials, which typically report cure rates <80%, provide an opportunity to compare biomarker responses in individuals who achieve SVR versus those who do not. In a treatment-shortening study from Vietnam, we evaluated changes in liver enzymes after DAA therapy. We then analyzed a larger UK study population to see whether our findings were replicated.

METHODS

This diagnostic accuracy study was STARD compliant[10] (Supplemental Table S1, http://links.lww.com/XCL/A8). Trial registrations and ethical permissions are provided with both published manuscripts.[11,12]

In SEARCH-1 (Vietnam), genotype 1 or 6-infected adults with mild liver disease (FibroScan score ≤7.1 kPa) received 4 or 8 weeks of sofosbuvir and daclatasvir therapy according to whether HCV RNA was below or above 500 IU/mL after 2 days of treatment. HCV RNA was measured at regular intervals until end of follow-up (EOT + 12 wk) or until treatment failure if it occurred first (Supplemental Figures S1 and S3, http://links.lww.com/XCL/A8). Of 52 adults recruited, 34 received 4 weeks of sofosbuvir/daclatasvir, 17 received 8 weeks, and 1 withdrew. SVR12 was achieved in 38/51 (75%). A total of 13 (25%) patients experienced virological relapse (between 21 and 84 days after EOT) and commenced retreatment within 2 weeks.

ALT and AST were measured at baseline and at EOT in all participants, at start of retreatment in those with virological relapse, and at EOT + 12 in those without evidence of treatment failure. We analyzed change in ALT and AST from EOT to EOT + 12 (ΔALT and ΔAST) in participants who were cured and from EOT to retreatment day zero (RTD0) in participants who failed treatment. Patients with ALT or AST greater than twice the upper limit of normal (>2×ULN) at EOT were excluded on the basis that this would ordinarily prompt HCV RNA testing.[13] We calculated median ΔALT and ΔAST [and interquartile ranges (IQR)] in patients according to whether their treatment was successful or unsuccessful and used Wilcoxon rank-sum test to compare outcomes. We also compared enzyme levels at baseline, EOT, and decline on treatment and performed genotype-specific analysis. We evaluated sensitivity and specificity of any increase in ALT (ΔALT > 0 IU/L) or any increase in AST (ΔAST > 0 IU/L) compared with gold standard of HCV RNA > LLOQ at EOT + 12 (or nearest available time point).

In a second study population, we tested the hypothesis that any increase in ALT or AST between EOT and EOT + 12 is a sensitive marker of treatment failure. STOPHCV1 (UK) was a randomized trial that assessed variable ultrashort-course treatment (4–8 weeks based on pretreatment viral load) versus 8 weeks of fixed-duration therapy with ombitasvir, paritaprevir, ritonavir +/− dasabuvir, +/− ribavirin (1:1).[14] Of 199 individuals under follow-up until EOT + 12, SVR12 was achieved in 141 (71%), with 58 individuals experiencing virological rebound at or before this time point (Supplemental Figures S2 and S4, http://links.lww.com/XCL/A8). ALT and AST were tested at baseline and EOT in all participants and at start or retreatment or EOT + 12 in those with or without evidence of virological rebound, respectively. We repeated the performance analysis of ΔALT and ΔAST used in SEARCH-1.

RESULTS

Patient characteristics are shown in (Supplemental Table S2 http://links.lww.com/XCL/A8). Both study populations had mild liver disease (FibroScan scores ≤ 7.1 kPa) and median ALT and AST levels within the normal range. Study populations differed in terms of genotypes, sex, ethnicity, HIV co-infection, and i.v. drug use.

In SEARCH-1, ALT and AST data were available for 48 participants (Figure 1), and data for treatment

		SEARCH-1	STOPHCV1
ALT	ALT data	48	196
	Cures	35	139
	Treatment failures	13	57
	Median ΔALT (IQR) Cures	-2 IU/L (-6, +2)	0 IU/L (-2, +5)
	Median ΔALT (IQR) Failure	+17 IU/L (+8, +38)	+41 IU/L (+20, +85)
	Sensitivity (95% C.I.)	92% (64 – 99.8)	100% (93.7, 100%)
	Specificity (95% C.I.)	66% (48 – 81%)	51.1% (42.4 - 59.7%)
	PPV (95% C.I.)	50% (29 – 71%)	46% (37 – 55%)
	NPV (95% C.I.)	96% (79 - 100)	100% (95 – 100%)
	AUROC (95% C.I.)	0.95 (0.87-1.00)	0.96 (0.94 -0.99)
AST	AST data	48	173
	Cures	35	120
	Treatment failures	13	53
	Median ΔAST (IQR) Cures	-1 IU/L (-3, +1)	+2 IU/L (-1, +5)
	Median ΔAST (IQR) Failure	+12 IU/L (+6, +16)	+23 IU/L (+13, +49)
	Sensitivity (95% C.I.)	100% (75 – 100%)	98.1% (89.9, 99.9%)
	Specificity (95% C.I.)	66% (48 – 81%)	35.8% (27.3, 45.1%)
	PPV (95% C.I.)	52% (31 -72%)	40% (32 – 49%)
	NPV (95% C.I.)	100% (85 – 100%)	98% (88 – 100%)
	AUROC (95% C.I.)	0.96 (0.91 - 1.00)	0.92 (0.88 - 0.96)

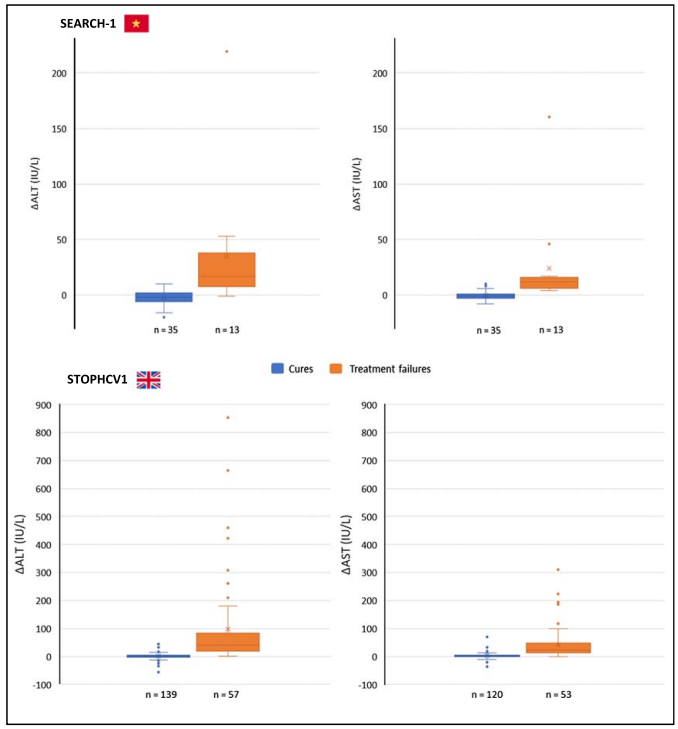

FIGURE 1 Performance analysis of ΔALT and ΔAST from EOT to EOT + 12 in cures and treatment failures in SEARCH-1 and STOPHCV1.

failures were from a median of 10 weeks after EOT (IQR = 6, 10). Median ΔALT and ΔAST were negative in cured patients but elevated when treatment failed [median ΔALT (IQR): −2 IU/L (−6, + 2)] versus + 17 IU/L (+ 7.5, + 38) ($p < 0.001$). Difference was significant in genotype 6 and non-genotype 6 infections (Supplemental Table S3, http://links.lww.com/XCL/A8), but we found no evidence of difference between groups in ALT or AST levels at baseline, EOT, or in transaminase decline on therapy (Supplemental Table S4, http://links.lww.com/XCL/A8). Overall, 12/13 and 13/13 patients who did not achieve SVR had an increase in ALT and AST between EOT and EOT+12, compared with 12/35 who cured. The one patient who did not have a rise in ALT accompanying virological rebound at EOT + 12 (HCV RNA = 3390 IU/mL; ΔALT = −1 IU/L) had a clear rise in ALT at EOT + 14 weeks (RTD0; HCV RNA = 125,032 IU/mL; ΔALT + 46 IU/L).

In STOPHCV1, 197 had evaluable ALT data and one patient was excluded on prespecified grounds of having an ALT rise > 2×ULN at EOT. Overall, 139/196 (71%) achieved SVR and 57 (29%) did not. ALT data for treatment failures were from a median of 10 weeks after EOT (IQR = 8, 13). An increase in ALT (ΔALT > 0 IU/L) after EOT was 100% sensitive (95% CI: 94–100) and 51% specific (95% CI: 42–60) for detecting treatment failure. A total of 173 participants had AST data (87%). ΔAST > 0 IU/L was 98% (89.9–100) sensitive and 36% (27.3–45.1) specific. Only one patient did not have a corresponding rise in AST around time of treatment failure: virological rebound was detected at EOT + 6 weeks, and ΔAST was 0 IU/L at EOT + 8 weeks (RTD0). Areas under receiver-operator curves demonstrated that ΔALT and ΔAST are excellent markers for identifying treatment failure (Supplemental Figures S5 and S6, http://links.lww.com/XCL/A8), with a negative predictive value exceeding 98% with standard rates of cure.

DISCUSSION

In mild liver disease, an increase in ALT or AST > 0 IU/L within a median of 10 weeks after EOT is highly sensitive for detecting treatment failure. This represents important proof of concept that could have a major impact in reducing treatment costs and decentralizing care. ALT testing is cheap ($2–$5 in Vietnam), does not entail additional visits or investigations, and can be performed in most laboratories. Novel point-of-care ALT tests from finger prick specimens could negate the need for a laboratory entirely.[15] Assuming a positive predictive valueof 46% (Figure 1), a negative predictive value of 100%, and a cure rate of 95%, this screening strategy would reduce NAT by 51%. In Vietnam, this translates to a saving of US$18–$46,000 per thousand patients treated (equivalent to ~36–90 courses of DAA therapy). This strategy could be used alongside emerging point-of-care HCV RNA platforms to facilitate treatment at primary health facilities or harm reduction sites.[1]

The main strength of our study is that our findings were replicated in two independent populations, with

differing demographics, genotypes, and antivirals. A higher median ΔALT and ΔAST after EOT in individuals not achieving SVR was observed in the UK study population in which alcohol abuse, illicit substance abuse, and HIV coinfection were more commonly reported (Supplemental Table S2, http://links.lww.com/XCL/A8). A major limitation is that all participants had mild liver disease and were treated with short-duration therapy. Our findings should be tested in the context of cirrhosis (where transaminase dynamics are altered and consequences of a false-negative result may be more serious) as well as with standard treatment durations with other WHO-approved antiviral regimens. In addition, timing of ALT/AST testing was earlier than EOT12 in most patients who failed to achieve SVR (median 10 wk after EOT (IQR: 8, 13). Despite these limitations, our data indicate that an increase in ALT or AST >0 IU/L after EOT is a highly sensitive marker of treatment failure, with potential to reduce costs and complexity of HCV care.

AUTHOR CONTRIBUTIONS

Barnaby Flower: designed the study, conducted the analysis, and wrote the manuscript. Phuong Nguyen Thi Ngoc: conducted the analysis. Leanne McCabe: curated and verified the data and assisted the analysis. Chau Le Ngoc, Thu Vo Thi, Hang Vu Thi Kim, Thuan Dang Trong, and Motiur Rahman: oversaw data collection and review of manuscript. Guy Thwaites, Ann Sarah Walker, Le Manh Hung, Nguyen Van Vinh Chau, and Jeremy Day: provided study oversight. Graham S. Cooke and Ann Sarah Walker: designed the clinical trials. Graham S. Cooke and Jeremy Day: provided study oversight and assisted with writing and review of the manuscript.

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CONFLICTS OF INTEREST

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