ISSN: 2754-6691

Journal of Internal Medicine Research & Reports

SCIENTIFIC Research and Community

Research Article

Open Access

The Association between Urinary Alcohol Metabolites on Hepatitis C Treatment and Response

Aaron Gerard Issac[1*], Yun Han Hannah Wang[2], Anand S. Shah[1,3] and Emily Cartwright[1,4]

[1]Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

[2]Emory University School of Public Health, Atlanta, GA, USA

[3]Division of Digestive Disease, Joseph Maxwell Cleland Atlanta VA Medical Center, Atlanta, GA, USA

[4]Division of Infectious Disease, Joseph Maxwell Cleland Atlanta VA Medical Center, , Atlanta, GA, USA

ABSTRACT

Background: Direct-acting antiviral (DAA) medications for the treatment of chronic hepatitis C virus (HCV) infection has achieved higher rates of sustained virologic response (SVR) with shorter treatment durations and no alcohol abstinence prerequisite. Previous therapies required alcohol abstinence for at least 6 months.

Methods: Our retrospective cohort study in Veterans with chronic HCV infection presenting for care at the Joseph Maxwell Cleland Atlanta VA medical center (AVAMC) between 1/1/2015 – 11/29/2017 examined the relationship between alcohol use, DAA initiation, and SVR.

Results: The cohort included 1763 people that were mostly males (97%) with a mean age of 63 years and 70% Black. In multivariate analysis, the odds of receiving DAA were 0.7 (95% CI: 0.674, 0.9; p=0.0013) in those with "detectable" alcohol metabolites compared with those who had "undetectable" alcohol metabolites. The odds of achieving SVR were 0.7 (95% CI: 0.5, 1.0; p=0.0525) in those with "detectable" alcohol metabolites. Overall, 86% of patients who received DAA therapy achieved SVR.

Conclusions: Alcohol use categorized using urine alcohol metabolite testing, during the study period was associated with a significantly lower odds of receiving DAA therapy but had no statistical significance on the odds of achieving SVR. While patients with chronic hepatitis C should be counseled on the risks of alcohol use, it is not associated with lower likelihood of achieving SVR and should not preclude the initiation of DAA therapy.

***Corresponding author**

Aaron Gerard Issac, MD, Department of Medicine, Emory University School of Medicine, 2015 Uppergate Dr, Atlanta, GA 30307, USA. Tel:214-843-8142.

Received: December 29, 2023; **Accepted:** January 01, 2024; **Published:** January 11, 2024

Keywords: Direct acting antivirals, Ethyl sulfate, Ethyl glucuronide, Veterans, Hepatitis C

Introduction

In the United States an estimated 2.4 million Americans have chronic hepatitis C [1]. Acute infection with hepatitis C virus (HCV) is often asymptomatic and can clear spontaneously, though 75-85% of people will develop chronic HCV infection [2]. If left untreated, hepatitis C can lead to liver cirrhosis, hepatocellular carcinoma (HCC), and death. Complications from chronic HCV infection often develop after decades of infection [3].

The goal of chronic HCV treatment is to achieve a sustained virologic response (SVR), defined as an undetectable HCV RNA level at least 12 weeks after treatment completion. Achieving SVR is a marker for cured HCV infection [4]. Prior to 2014, the primary treatment regimens for chronic HCV infection included injectable pegylated interferon (PEG-IFN) and ribavirin (RBV), a highly toxic and medically complex regimen that few people were considered treatment candidates for, and tolerability was poor for those initiated on treatment. Specifically, alcohol use was contraindicated with PEG-IFN and RBV use and a 6-month period of alcohol abstinence prior to treatment was required. The 2009 American Association for the Study Liver Diseases (AASLD) Practice Guidelines stated that "[Current users of illicit drugs or alcohol] should be abstinent for a minimum period of 6 months" [5].

In 2014, the Food and Drug Administration approved new oral medications known as direct-acting antivirals (DAA) that could be used without PEG-IFN and RBV [6]. The new DAA regimens were given for shorter durations and the safety, tolerability, and efficacy were significantly improved [7]. By 2019, AASLD guidelines no longer required alcohol abstinence prior to treatment [8].

Currently, more than 95% achieve SVR with DAA treatment [9]. By reducing barriers and initiating treatment sooner, complications from chronic HCV infection can be avoided [3].

The Veterans Health Administration (VA) is a federal healthcare system that provides care to eligible and enrolled US Veterans. VA is the largest single provider of HCV care in the United States [10]. Among patients in the VA, chronic HCV is three times more prevalent compared with the general U.S. population [11]. In the VA, patients have high rates of psychiatric disorders and substance abuse and 67.8% of VA patients were not eligible for PEG-IFN and RBV treatment [12]. In 2013, only 23% of HCV patients in the VA had ever received interferon-based antiviral treatment [3].

Many patients were ineligible for interferon-based therapy because of alcohol use. We sought to examine the prevalence of alcohol use and the association of alcohol use with receipt of DAA therapy and achievement of SVR among patients with chronic HCV infection at the Joseph Maxwell Cleland Atlanta VA Medical Center Atlanta VA medical center (AVAMC).

Materials and Methods

The data was obtained from the Atlanta VA clinical case registry (CCR) system, and Institutional Review Board (IRB) approval was obtained. The CCR connects with the VA's electronic medical record system. Each VA has local registry coordinators to help review medical records to review potential HCV-infected Veterans using positive antibody test results and/or diagnosis codes based on International Classification of Diseases, tenth revision (ICD-10) codes. Patients with confirmed HCV infections are then added to the CCR, where data on demographics, laboratory tests, and prescriptions are recorded. To conduct this analysis, reports using different criteria were exported and data on medication, alcohol metabolite test results, viral load test results, and demographic information such as age, sex, and race were obtained from 1/1/2015 to 11/29/2017. The datasets were merged into a single dataset for analysis. To detect recent alcohol use, urine alcohol metabolite testing was performed for those presenting for routine HCV clinical care. Urine alcohol metabolite testing is also routinely performed for those on chronic controlled substances such as narcotics and is used for monitoring in the substance use treatment program including those on methadone or buprenorphine. Ethyl glucuronide (EtG) or ethyl sulfate (EtS) are alcohol metabolites that can be detected up to 80 hours after alcohol consumption [13]. Alcohol use categories were created using the following criteria:
- Detectable: if EtG or EtS was ever greater than or equal to 100 ng/mL
- Undetectable: if EtG and EtS are less than 100 ng/ml

Patients with multiple urine alcohol metabolite tests were considered to have a positive screen if any test result showed a detectable level. To define those who received DAA treatment, we selected patients who were tested for alcohol metabolites and received any of the following during the study period: Daclatasvir (DCV), dasabuvir/ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir (EBR/GZR), glecaprevir/pibrentasvir (GLE/PIB), ledipasvir/sofosbuvir (LDV/SOF), simeprevir (SIM), sofosbuvir (SOF), sofosbuvir/velpatasvir (SOF/VEL), and sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX). Patients were considered to achieve SVR if their most recent HCV RNA test was undetectable. Patients that had missing data in the dataset were manually chart reviewed, and excluded if variables such as viral load were missing.

Data analysis was conducted using SAS version 9 (Cary, NC). Multivariable logistic regression analysis was conducted, controlling for race and age. Because the study population was predominantly male, sex was not included as part of the model.

Results

In our retrospective cohort study, we identified 1876 patients, 1822 (97.1%) were male with an average of 62.9 ± 6.5 years. Most patients (n=1300 , 69.2%) identified as Black or African American race (Table 1).

Table 1: Baseline Characteristics

Number of Patients	Overall (n=1,763)
Age, years (mean)	63
Sex	
Male	1,711 (97%)
Female	52 (3%)
Race	
Black or African American	1,227 (70%)
White	454 (26%
Other	82 (4%)
Type of Treatment	
Ledipasvir/Sofosbuvir	665 (56%)
Elbasvir/Grazoprevir	292 (25%)
Sofosbuvir/Velpatasvir	123 (10%)
Other	113 (9%)

Of the 1876 patients, 1764 (94%) patients had alcohol metabolite tests within the study period. All patients had at least one alcohol metabolite test (57.7% had at least two observations, 18.8% had four observations, and 23.5% had more than 6 observations). In assessing the prevalence of alcohol use, 599 (34.0%) of the 1764 patients who were tested had at least one detectable urine alcohol metabolite test. We found that 1306 (69.6%) received DAA treatment, with a majority of patients taking either LDV/SOF (51.8%) or EBR/GZR (22.5%). During the study period, 1113 (85.8%) patients achieved SVR. Within the cohort there were 36 deaths.

Receipt of HCV Direct-acting Antiviral Treatment

The odds of receiving DAA was 0.708 (95% CI: 0.574, 0.873) for those with detectable alcohol metabolites (Figure 1) compared with those with undetectable alcohol metabolites. The odds of receiving DAA was 1.608 (95% CI: 1.289, 2.006) for Blacks compared to Whites.

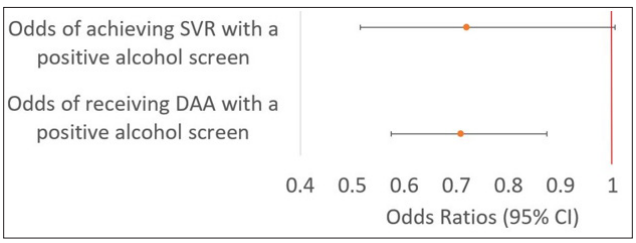

Figure 1: Odds of achieving SVR and receiving DAA therapy with detectable alcohol metabolites

The odds of achieving SVR was 0.719 (95% CI: 0.515, 1.004; p=0.0525) for those with detectable alcohol metabolites. The odds of achieving SVR was 1.770 (95% CI: 1.251, 2.504; p=0.0013) for Blacks compared to Whites. Other races compared to whites and age groups did not have statistical significance in odds of achieving SVR (p=0.6255 and 0.4739, respectively).

Discussion

We found that having detectable alcohol metabolites was associated with a lower odd of receiving DAAs. In addition, despite lower odds of receiving DAAs, alcohol use by urinary metabolites was not associated with lower rates of SVR.

Haque et al. (2023) performed a national VA study of 133,753 patients born between 1945 to 1965 with HCV investigated alcohol use and receipt of DAA therapy among patients with HCV [14]. To assess for alcohol use, the study investigators used the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) questionnaire in combination with ICD-9 and ICD-10 diagnostic codes for alcohol use disorder. They concluded that patients with a history of AUD or with current AUD were less likely to receive DAA therapy compared with patients with lower risk drinking. In comparison, our study is a single center VA study that used urinary alcohol metabolites to compare any alcohol consumption instead of stratification of risk of alcohol abuse. In our study, a positive urinary alcohol metabolite screen was associated with lower rates of DAA initiation. This finding may be due to the fact that, historically, alcohol use complicated HCV treatment (PEG-IFN and RBV) and was a contraindication per prior treatment guidelines. For providers, other reasons for delays in initiation of HCV treatment are due to minimal experience with therapies, low likelihood of referrals to specialists for therapies, and poor provider-patient relationship. In addition, patients may not initiate treatment because of lack of awareness of current treatment availability and stigma [15].

This study found no statistical significance on odds of achieving SVR for those who used alcohol during the study period, with 85.8% of AVAMC patients achieving SVR. Published DAA clinical trials report 95% achieving SVR, however, those studies often report a modified intention to treat analysis; our study counted every person missing an HCV RNA test as having not achieved SVR. In this study there was no difference in virologic cure amongst those with evidence of recent alcohol use versus those who did not have recent alcohol use. Tsui et al. (2016) published a retrospective cohort study using national VA data of 10,387 patients who initiated DAAs and had complete AUDIT-C screening [16]. They categorized patients as either abstinent, low level drinkers, or unhealthy drinkers using AUDIT-C scores and evaluated SVR rates. Despite differences in alcohol use all 3 categories showed SVR rates of at least 90% or higher, which would reduce the risk of negative outcomes such as HCC and cirrhosis. Our study had similar conclusions with using urinary alcohol metabolites to determine recent alcohol use.

In our study 34% of Veterans with chronic HCV infection at the AVAMC were found to have recent alcohol use using urine alcohol metabolite testing during the study period. This study differs from other studies in that alcohol use is defined using biomarkers instead of information obtained from diagnostic codes or self-report. Though there are a multitude of different professional groups that define alcohol use, one of the most prevalent terms is alcohol use disorder, defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. This is often used for diagnostic coding. In addition, alcohol screening according to United States Preventive Services Task Force (USPSTF) is most accurate using either the AUDIT-C or the Single Alcohol Screening Question [17]. Using subjective questionnaires and DSM-5 criteria can lead to differences in diagnosis even with similar alcohol consumption. Vickers-Smith et al. (2023) showed in a sample of 700,000 Veterans that black and Hispanic Veterans were more likely to have a diagnosis of AUD even with similar alcohol use to white Veterans [18,19]. In other systems such as state Medicaid, DAA use may still require a negative screening period of alcohol and substance use [20]. We found that current alcohol use, defined using urinary biomarkers, was not associated with reduced likelihood of SVR. Self-reported alcohol methods may also underestimate alcohol use due to recall bias and concerns for confidentiality and social acceptability [20,21]. Serum or urine alcohol biomarkers can provide a more objective determination of alcohol use though are more expensive and limited by no clear guidelines to stratify alcohol use. In addition, single measurements may over or underestimate alcohol use depending on a patient's last drinking episode. Initial alcohol use markers such as Aspartate Aminotransferase and Gamma-Glutamyltransferase differed by ethnicity, given differences in metabolism [22]. Newer alcohol use markers such as EtG and EtS are metabolites that are not affected by age, ethnicity, and severity of liver disease [23]. While urinary alcohol markers are only positive up to 80 hours after alcohol consumption, newer serum markers such as phosphatidylethanol (PEth) can detect alcohol up to 12 days after a single instance of alcohol consumption [24].

Limitations to this study include the use of urinary alcohol metabolite data being used to assess alcohol use as it only evaluates recent alcohol use. Research suggests EtG and EtS can be used as effective biomarkers for determining abstinence but cannot determine if someone has alcohol use disorder [25]. Our study looked at recent alcohol use and the pattern and level of alcohol consumption was not assessed. Other limitations to this study include that this is a single center study with a predominantly male population. Veterans who had care outside the VA were not assessed, and patients who did not complete treatment were included. Though our data showed decreased alcohol use was associated with a lower odd of receiving DAAs it does not include why the patient did not receive DAAs. Retrospective data lacks information on why treatment was not initiated and lacks data on adherence, medical comorbidities, degree of liver disease and other factors that influence why someone would be prescribed DAAs and likelihood of achieving cure.

Conclusion

Aligning with the VA's treatment consideration guidelines, alcohol use should not automatically exclude patients from HCV treatment. As our study showed, detectable alcohol use was associated with a lower likelihood of receiving DAAs; however, alcohol use was not associated with lower rates of SVR. Providers should determine whether patients can initiate DAA treatment after careful examination of a patient's medical history. However, providers should encourage patients to reduce or stop alcohol use due to potential risk of non-adherence and increased risk of cirrhosis and HCC. Since curing HCV has been shown to reduce the risk of HCC and cirrhosis, prescribing DAA therapy to a patient with concurrent alcohol use disorder can reduce risk of adverse liver-related outcomes.

Statements

- Guarantor of the article: Emily Cartwright, MD, author has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis
- Data availability: All relevant data is contained within the article. Further inquiries can be directed to the corresponding author.
- All data was collected and used in line with institutional IRB protocols, and IRB approval was obtained for this study.

References

1. Office of Infectious Disease and HIV/AIDS Policy (OIDP. Data and Trends [Internet]. HHS.gov. 2016. Available from: https://www.hhs.gov/hepatitis/learn-about-viral-hepatitis/data-and-trends/index.html
2. Chen SL, Morgan TR (2006) The natural history of hepatitis C virus (HCV) infection. International journal of medical sciences 3:47.
3. Beste LA, Ioannou GN (2015) Prevalence and treatment of chronic hepatitis C virus infection in the US Department of Veterans Affairs. Epidemiologic reviews 37: 131-143.
4. Burgess SV, Hussaini T, Yoshida EM (2016) Concordance of sustained virologic response at weeks 4, 12 and 24 post-treatment of hepatitis c in the era of new oral direct-acting antivirals: a concise review. Annals of hepatology 15: 154-159.
5. Ghany MG, Strader DB, Thomas DL, Seeff LB (2009) Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 49: 1335-1374
6. Chan K, Lai MN, Groessl EJ, Hanchate AD, Wong JB, et al. (2013) Cost effectiveness of direct-acting antiviral therapy for treatment-naive patients with chronic HCV genotype 1 infection in the veterans health administration. Clinical Gastroenterology and Hepatology 11: 1503- 1510.
7. Wang LS, D'Souza LS, Jacobson IM (2016) Hepatitis C-a clinical review. Journal of medical virology 88: 1844-1855.
8. Ghany MG, Morgan TR, AASLD-IDSA (2020) hepatitis C guidance panel. Hepatitis C guidance 2019 update: American Association for the Study of Liver Diseases–Infectious Diseases Society of America recommendations for testing, managing, and treating hepatitis C virus infection. Hepatology 71: 686-721.
9. Zoulim F, Liang TJ, Gerbes AL, Aghemo A, Deuffic-Burban S, et al. (2015) Hepatitis C virus treatment in the real world: optimising treatment and access to therapies. Gut 64: 1824.
10. Belperio PS, Chartier M, Ross DB, Alaigh P, Shulkin D (2017) Curing hepatitis C virus infection: best practices from the US Department of Veterans Affairs. Annals of internal medicine 167: 499-504.
11. Gonzalez R, Park A, Yakovchenko V, Rogal S, Chartier M, et al. (2021) HCV elimination in the US Department of Veterans Affairs. Clinical Liver Disease 18: 1-6.
12. Talal A H., LaFleur J, Hoop R, Pandya P, Martin P, et al. (2013) Absolute and relative contraindications to pegylated-interferon or ribavirin in the US general patient population with chronic hepatitis C: results from a US database of over 45 000 HCV-infected, evaluated patients. Alimentary pharmacology & therapeutics 37: 473-481.
13. Ethyl Glucuronide and Ethyl Sulfate, Urine, Quantitative | ARUP Laboratories Test Directory [Internet]. ltd.aruplab.com. Available from: https://ltd.aruplab.com/Tests/Pub/2007909
14. Haque LY, Fiellin DA, Tate JP, Esserman D, Bhattacharya D, et al. (2022) Association between alcohol use disorder and receipt of direct-acting antiviral hepatitis C virus treatment. JAMA network open 5: e2246604.
15. Mc Gowan CE, Fried MW (2012) Barriers to hepatitis C treatment. Liver international 32: 151-156.
16. Tsui JI, Williams EC, Green PK, Berry K, Su F, et al. (2016) Alcohol use and hepatitis C virus treatment outcomes among patients receiving direct antiviral agents. Drug and alcohol dependence 169: 101-109.
17. Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, et al. (2018) Screening and behavioral counseling interventions to reduce unhealthy alcohol use in adolescents and adults: US Preventive Services Task Force recommendation statement. Jama 320: 1899-1909.
18. Vickers-Smith R, Justice AC, Becker WC, Rentsch CT, Curtis B, et al. (2023) Racial and ethnic bias in the diagnosis of alcohol use disorder in veterans. American Journal of Psychiatry 180: 426-436.
19. Waters P, Broder T (2018) Rationing Care: Barriers to Direct-Acting Antiviral Treatment in Medicaid Treatment Criteria. Clinical Liver Disease 12: 122-124.
20. Del Boca FK, Darkes J (2003) The validity of self-reports of alcohol consumption: state of the science and challenges for research. Addiction. 98: 1-2.
21. Simons JS, Wills TA, Emery NN, Marks RM (2015) Quantifying alcohol consumption: Self-report, transdermal assessment, and prediction of dependence symptoms. Addictive behaviors. 50: 205-212.
22. Stewart SH (2002) Racial and ethnic differences in alcohol-associated aspartate aminotransferase and γ-glutamyltransferase elevation. Archives of internal medicine 162: 2236-2239.
23. Cabezas J, Lucey MR, Bataller R (2016) Biomarkers for monitoring alcohol use. Clinical liver disease 8: 59-63.
24. Schröck A, Thierauf-Emberger A, Schürch S, Weinmann W (2017) Phosphatidylethanol (PEth) detected in blood for 3 to 12 days after single consumption of alcohol-a drinking study with 16 volunteers. International journal of legal medicine 131: 153-160.
25. Jastrzębska I, Zwolak A, Szczyrek M, Wawryniuk A, Skrzydło-Radomańska B, et al. (2016) Biomarkers of alcohol misuse: recent advances and future prospects. Gastroenterology Review/Przegląd Gastroenterologiczny 11: 78-89.

Copyright: ©2024 Aaron Gerard Issac, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.