mhc
MENTAL HEALTH CLINICIAN

ORIGINAL RESEARCH Open Access

Evaluating psychiatric outcomes associated with direct-acting antiviral treatment in veterans with hepatitis C infection

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How to cite: Sackey B, Shults JG, Moore TA, Rogers R, Mehvar M, King JG. Evaluating psychiatric outcomes associated with direct-acting antiviral treatment in veterans with hepatitis C infection. Ment Health Clin [Internet]. 2018;8(3):116-21. DOI: 10.9740/mhc.2018.05.116.

Abstract

Introduction: Approximately 70% of veterans with hepatitis C virus infection have at least one psychiatric illness. The advent of direct-acting antiviral (DAA) therapy provided an alternative to interferon-alpha regimens and revolutionized treatment, however, the extent of psychiatric effects attributed to these agents are unclear. The primary objective of this pilot study was to prospectively analyze psychiatric outcomes, specifically depression, in veterans with hepatitis C virus infection who are initiated on DAA therapy.

Methods: In this single center, prospective cohort study, psychiatric outcomes were analyzed using Patient Health Questionnaire assessments at baseline and weeks 4, 8, and 12 of complete DAA treatment. Outcome analysis were stratified based on specific DAA therapy and preexisting mental illness (mental health [MH] subjects and non-MH subjects), with a sub-analysis of major depressive disorder patients.

Results: Analysis included 48 patients, majority males (96%), with a mean age of 59.4 years (±8.0). Twenty-four (50%) patients had a preexisting MH diagnosis, with major depressive disorder being the most common MH diagnosis (50%, n = 12). Despite a trend toward improvement, no significant changes in questionnaire scores after 12 weeks of DAA therapy were observed for all patient groups ($P > .05$). Neither MH subjects nor non-MH subjects displayed a significant change in questionnaire scores from baseline to end of treatment ($P > .05$). No patients required acute psychiatric interventions during DAA treatment.

Discussion: Treatment with DAA therapy was not associated with psychiatric decompensation. Data from this pilot study supports the safe utilization of DAA therapy in hepatitis C virus patients with preexisting MH illness as it appears to be devoid of depressive and psychiatric side effects.

Keywords: mental health, hepatitis C, pharmacist, psychiatry, depression, PHQ-9, infectious disease, antiviral, direct-acting antiviral

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Disclosures: Nothing to disclose.

Introduction

It is estimated that 2.7 to 3.9 million people in the United States are living with hepatitis C virus (HCV).[1] Rates of mental illness among HCV patients are significantly higher than in the general population, with depression occurring at 25%, schizophrenia at 3.9%, and bipolar disorder at 2.6%.[2] Approximately 70% of veterans with HCV have at least 1 psychiatric illness, and the prevalence of HCV infection among veterans with severe psychiatric illness is 3 to 4 times the prevalence of HCV in the general veteran population.[3-7] Historically, interferon (IFN-α) based regimens were the standard of care for HCV. Despite its proven efficacy, IFN-α poses a considerable challenge for many psychiatric patients as it has been shown to contribute to several mental illnesses. Rates of IFN-α–induced depression range from 25% to 30%, which may also include suicidal ideation.[8] Additionally, ribavirin (RBV), a viral RNA polymerase inhibitor often coadministered with IFN-α, is independently associated with depressive symptoms, though the exact rate is unclear.[8-11] Due to the high comorbidity of psychiatric illness and HCV infection, associated adverse effects of HCV medications have traditionally led to reduced treatment initiation in the psychiatric population.[9-10] The approval of direct-acting antiviral (DAA) agents, however, revolutionized HCV treatment and eventually allowed for non–IFN-α–based regimens. With shorter treatment durations and improved side effect profiles, psychiatric and psychosocial contraindications to treatment are greatly reduced.[11-16] Additionally, the more favorable side effect profiles of DAA agents (ie, less blood dyscrasias and fatigue) has led to adherence rates as high as 96.2%, compared to 84.3% in IFN-free RBV-containing regimens and 77.6% in IFN- and RBV-containing regimens.[17]

Currently, the extent of psychiatric effects attributed to DAA agents is unclear; however, it is noted to be less than IFN-containing regimens.[18-20] Though data[8] suggests that DAAs overall confer a minimal risk of psychiatric adverse effects compared to IFN-based regimens, there is a paucity of data specifically analyzing neuropsychiatric complications of these agents. Additionally, it is unclear whether DAA therapy may exacerbate mood symptoms in patients with prior psychiatric history. It is important to note that many DAA studies excluded those with recent psychiatric hospitalization, suicide attempt, or psychiatric disability during clinical trials.[18-20] Moreover, assessment of psychiatric adverse effects in these studies did not utilize formal psycho-diagnostic tools.[8,18-20]

The objective of this pilot study is to prospectively analyze psychiatric outcomes, specifically depression, in veterans with HCV infection who are initiated on DAA therapy by quantitatively measuring the change in the 9-item Patient Health Questionnaire (PHQ-9) scores.

Methods

Study Design

This study was an institutional review board-approved prospective cohort study conducted at the South Texas Veterans Health Care System. Verbal consent was obtained upon initial patient encounter (requirement for written consent was waived by the institutional review board); there was no incentive/payment for participation in this study. The study population included HCV-infected veteran patients, 18 years and older, who were initiated on a 12-week DAA therapy. The population included those with or without a preexisting mental health (MH) diagnosis. Patients were excluded if they were receiving current treatment with an IFN-α– or RBV-based regimen, had non–HCV-related liver disease (except coexisting alcoholic liver disease), had a previous failure with a DAA agent (at least 4 weeks of therapy), or had significant life-threatening diseases that may prohibit completion of therapy (ie, malignancies and any incapacitating lung, cardiac, renal, or autoimmune disease).

Data Collection

Data was collected using the self-administered PHQ-9 screening tool during HCV shared medical appointments and face-to-face clinic visits, which occurred at weeks 0, 4, 8, and 12 (end of treatment or EOT). Additional data collection was conducted through electronic health records, which included demographic information (age, sex, race, marital status, and employment), components of patients' MH (current or past MH diagnosis, specific MH diagnosis, receiving active MH treatment, established MH provider, prior psychiatric hospitalization, history of substance abuse), and components of patients' HCV infection (genotype, fibrosis score, selected DAA treatment, previously failed therapies, treatment naïve, previous IFN-α/RBV use). Additionally, patients' charts were reviewed weekly for any psychiatric interventions throughout DAA treatment (ie, medication adjustments, MH referral).

Outcomes

The primary outcome was change in MH status from baseline to EOT as measured by PHQ-9 scores in the total study population. Secondary outcomes included subgroup analysis of MH status changes based on specific DAA treatment, preexisting mental illness (MH versus non-MH subjects), and diagnosis of major depressive disorder (MDD). To capture psychiatric outcomes not directly reflected by PHQ-9 scores, ancillary psychiatric interventions were also assessed during treatment period which included medication adjustments, psychiatric hospitaliza-

tions, emergency department visits, documented crisis line contact, and MH referrals.

Data Analysis

A paired *t* test (Wilcoxon signed rank for non-parametric data) was used to analyze mean difference in MH status changes from baseline to EOT for primary and secondary outcomes. Descriptive statistics were used to analyze all continuous and nominal data. Last observation carried forward method was used to analyze missing data. Patients were excluded from the final analysis if they withdrew from treatment. Power was not calculated given that it was a pilot study with a relatively small sample size. Alpha level set at 0.05; all data was analyzed using SPSS version 22 (IBM Corp, Amonk, NY).

Results

A total of 62 HCV patients were evaluated for study inclusion during the study period. Of the 62 patients, 1 prematurely withdrew from treatment (alcohol relapse), 7 deferred treatment to a later date, and 6 were excluded (2 previously failed a DAA agent, 4 were concurrently receiving RBV). A total of 48 veterans met inclusion criteria and were analyzed for this study. Majority were white (52%) males (96%), with a mean age of 59.4 years (±8.0). Twenty-four (50%) patients had a preexisting MH diagnosis, with MDD being the most common MH diagnosis (50%). Regarding DAA treatment, 30 patients (63%) were prescribed elbasvir/grazoprevir, 14 (29%) were prescribed sofosbuvir/velpatasvir, and 4 (8%) were prescribed sofosbuvir/ledipasvir. Full patient characteristics can be found in Table 1.

TABLE 1: Baseline characteristics

Baseline Characteristics	N = 48
Males, No. (%)	46 (96)
Age, y (mean ± SD)	59.4 ± 8.0
Ethnicity, No. (%)	
White	25 (52)
Black or African American	12 (25)
Hispanic	10 (21)
Current or prior MH diagnosis, No. (%)	24 (50)
Specific MH diagnosis, No. (%) – among those with MH diagnosis	
Major depressive disorder	12 (50)
Posttraumatic stress disorder	8 (33)
Anxiety disorder	6 (25)
Bipolar disorder	4 (16)
Schizophrenia/psychotic disorder	2 (8)
Presence of 2 or more MH diagnoses, No. (%)	14 (29)
Currently receiving treatment for MH condition, No. (%)	19 (79)
Prior psychiatric hospitalization, No. (%)	13 (27)
Current or prior substance abuse, No. (%)	29 (60)
Hepatitis C virus genotype, No. (%)	
1a	27 (56)
2	8 (16)
3	6 (13)
Fibrosis score, No. (mean ± SD)	1.7 ± 0.88
Liver cirrhosis, No. (%)	9 (19)
Treatment naïve, No. (%)	40 (84)
Previously failed Peg-interferon therapy, No. (%)	8 (16)
Selected direct-acting antiviral treatment, No. (%)	
Zepatier (elbasvir/grazoprevir)	30 (63)
Epclusa (sofosbuvir/velpatasvir)	14 (29)
Harvoni (sofosbuvir/ledispavir)	4 (8)

MH = mental health.

There was a trend toward lower PHQ-9 scores from baseline to EOT for all subjects (see the Figure), however the mean change in scores was not statistically significant (mean change −1.06, $P = .14$). Similarly, subanalysis of MH subjects, non-MH subjects, and MDD patients demonstrated a reduction in mean PHQ-9 scores from baseline to EOT (mean change −1.29, −0.83, −1.08 respectively), however changes were not statistically significant (all $P > .05$). Subanalysis of the individual DAA treatment groups similarly did not reach statistical significance (all $P > .05$). See Table 2 for primary and secondary outcomes.

For the non-MH subjects, 1 patient required a MH consult for initiation of psychotherapy, and 1 patient initiated an agent to aid in sleep during the treatment period. For the MH subjects, 7 patients required a psychopharmacologic intervention (medication increase/initiation), and 1 patient required a MH referral. The majority of aforementioned psychopharmacologic interventions in MH patients were related to either sleep or anxiety concerns (n = 5, 71%); the remaining interventions appeared to be pre-scheduled medication titration for ongoing mood disturbances unrelated to HCV treatment. No patients in this study required acute psychiatric interventions (emergency department visits, psychiatric hospitalization) during the treatment period.

Discussion

Our study found no change in PHQ-9 scores from baseline to EOT for all subjects after administration of DAA treatment for HCV, however there were numeric trends favoring improving scores. Subanalysis of MH subjects, non-MH subjects, MDD patients, and specific DAA treatments all revealed similar results. The only exception

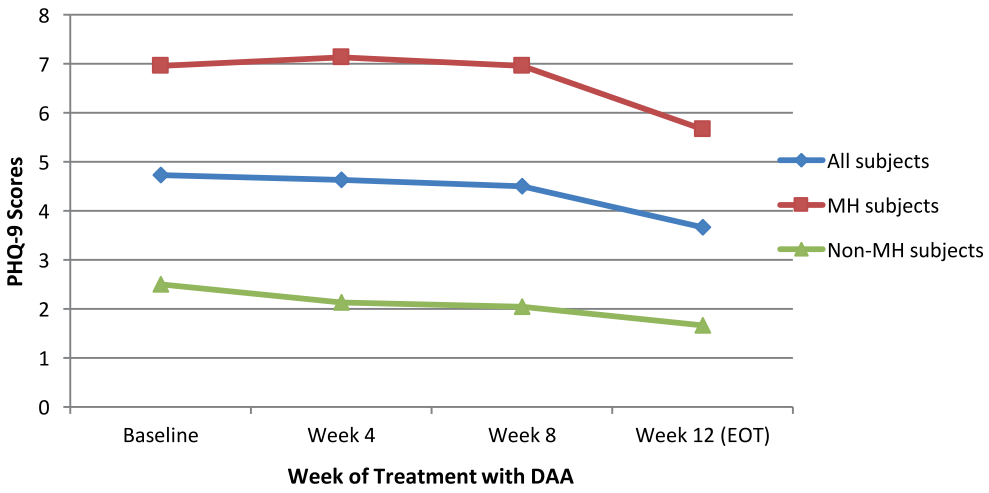

FIGURE: Patient Health Questionnaire (PHQ-9) scores through treatment with direct-acting antiviral (DAA) agents for all subjects, mental health (MH) subjects, and non-MH subjects; EOT = end of treatment

was those who were on sofosbuvir/ledipasvir which showed a slight increase in PHQ-9 scores from baseline; however, this may be skewed due to the small sample size in this group (n = 4). Analysis of psychiatric interventions through treatment revealed minimal psychopharmacological adjustments required. Majority of interventions were related to sleep/anxiety with no acute interventions. Data from our study suggest a lack of psychiatric decompensation associated with evaluated DAA treatment in veterans with HCV, with a potential for improved depressive symptoms.

The lack of observed mood decompensation may be explained by the differences in pharmacological properties of DAA agents compared to previous HCV treatment modalities. The mechanism of IFN-α induced psychiatric effect is thought to be related to peripheral inflammatory cytokines and is composed of two syndromes: a depression-specific syndrome (ie, depressed mood, melancholia, anhedonia, anxiety) and a neurovegetative syndrome (ie, fatigue, insomnia, and/or psychomotor slowness). These symptoms typically develop early and persist during IFN-α treatment.[21] Some of the neurovegetative components, namely fatigue and insomnia, are also seen in some of the DAA therapies including ledipasvir/sofosbuvir (4% to 18% fatigue; 3% to 6% insomnia) and sofosbuvir/velpatasvir (15% to 32% fatigue; 11% insomnia).[22,23] Despite the presence of these neurovegetative adverse effects, administration of DAA treatment did not lead to clinical or statistically significant depression in our study. According to Wichers et al,[24] proinflammatory cytokines, including exogenous IFN-α, has also been shown to upregulate the enzyme indoleamine 2,3-dioxygenase, which depletes tryptophan by converting it into kynurenine rather than serotonin. Elevated ratios of kynurenine/tryptophan has been associated with significant increases in Montgomery-Asberg Depression Rating Scale scores during IFN-α treatment.[24] The described role of neuroinflammation in depressive symptoms is consistent with the chronic stress model of depression, which implicates increased cytokine activity as a cause of depressive morbidity.[24] Direct-acting antivirals are devoid of pro-inflammatory properties,

TABLE 2: Primary and secondary outcomes

Group	Mean Baseline PHQ-9	Mean End of Treatment PHQ-9	Mean Change in PHQ-9 Scores	*P* Value
All subjects	4.72 ± 5.25	3.66 ± 4.74	−1.06	.14
MH subjects	6.95 ± 5.26	5.66 ± 4.76	−1.29	.33
Non-MH subjects	2.5 ± 5.30	1.66 ± 4.79	−0.83	.19
Major depressive disorder patients	7.16 ± 5.43	6.08 ± 4.68	−1.08	.53
Direct-acting antiviral treatment				
Zepatier (elbasvir/grazoprevir)	4.83 ± 5.30	3.9 ± 4.79	−0.93	.20
Epclusa (sofosbuvir/velpatasvir)	5.07 ± 5.34	3.35 ± 4.82	−1.71	.36
Harvoni (sofosbuvir/ledipasvir)	2.75 ± 4.83	3 ± 4.25	+0.17	.91

MH = mental health; PHQ-9 = Patient Health Questionnaire.

which may describe the lack of observed depressive symptoms.

Another important concept to consider in HCV patients is the potential for neuropsychiatric toxicities associated with the virus itself. Several studies[25-27] have demonstrated untreated HCV to be associated with significantly more neuropsychiatric complications compared to those who have cleared the virus, irrespective of extensive liver damage, substance abuse, and/or prior mental illness. The biological plausibility of this phenomenon has been illustrated through brain imaging, which shows increased neuroinflammation in those with HCV viremia versus healthy controls.[26] Hepatitis C viremia is thought to induce neuroinflammation through penetration and replication in the central nervous system, which results in altered metabolism and downstream neurotoxicity.[25-26] Additionally, untreated HCV-infected patients have been associated with elevated kynurenine/tryptophan ratios, similar to observed effects with IFN-α treatment.[24-26] The biological etiology for HCV-associated neurotoxicity may describe the improvement in PHQ-9 scores as the virus is eliminated with DAA treatment in our study. Similarly, Kraus et al[28] found that successful HCV eradication with IFN-α/RBV was associated with improved memory, vigilance, and working memory, however this was not observed during active treatment but rather occurred after 1 year of therapy. Potential for neuropsychiatric symptom resolution during treatment may be masked by the depressive symptoms induced by IFN-α/RBV therapy. Of note, virologic nonresponders showed no such improvements throughout treatment or at 1-year follow-up for that study.[28]

Not only does our study suggest a lack of mood disturbance associated with the evaluated DAA therapy, but it also highlights the importance of initiating HCV treatment, as evidenced by trends toward improved mood symptoms. Despite the high prevalence of substance abuse and MH patients in the HCV population, there continues to be a low number of patients who are screened and/or initiated on therapy.[29] Although cost remains a significant barrier to treatment, it is important to educate patients on the psychiatric burden of HCV and eliminate stigmas associated with therapy.

The primary limitations of this study were its small sample size, which was limited to a single site within the Veterans Health Administration population. Additionally, our findings were limited to the specific DAA agents evaluated in our study, which may not be generalizable to other DAA agents. Limitations in PHQ-9 assessment in non-MDD subjects may not accurately capture mood changes, however evaluations of other MH components revealed minimal psychiatric interventions required during DAA treatment.[30] Also, given that the patients presented with minimal to mild depressive symptoms based on the low baseline PHQ-9 scores, the magnitude of change and/or effects in severely depressed patients is unclear. Additionally, information on sustained virologic response rates were not obtained and thus correlations between HCV infection resolution and depression cannot be made. Moreover, this was a pilot study and thus the majority of our findings were hypothesis-generating and warrant further investigation with larger sample sizes. Future studies should aim to evaluate mood changes beyond the 12-week treatment period (ie, 4, 6, and 12 weeks after EOT) and changes in PHQ-9 scores in correlation with virologic response.

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