Suicidal and paranoid thoughts after starting hepatitis C virus treatment

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How would you handle this case?

Answer the **challenge questions** throughout this article

Ms. B, age 53, reports stopping her medication regimen after starting hepatitis C virus treatment because of new-onset suicidal ideation and paranoia. What is your treatment plan?

CASE Suicidal and paranoid

Ms. B, age 53, has a 30-year history of bipolar disorder, a 1-year history of hepatitis C virus (HCV), and previous inpatient psychiatric hospitalizations secondary to acute mania. She presents to our hospital describing her symptoms as the "worst depression ever" and reports suicidal ideation and paranoid thoughts of people watching and following her. Ms. B describes significant neurovegetative symptoms of depression, including poor sleep, poor appetite, low energy and concentration, and chronic feelings of hopelessness with thoughts of "ending it all." Ms. B reports that her symptoms started 3 weeks ago, a few days after she started taking sofosbuvir and ribavirin for refractory HCV.

Ms. B's medication regimen consisted of quetiapine, 400 mg at bedtime, fluoxetine, 40 mg/d, and lamotrigine, 150 mg/d, for bipolar disorder, when she started taking sofosbuvir and ribavirin. Ms. B admits she stopped taking her psychotropic and antiviral medications after she noticed progressively worsening depression with intrusive suicidal thoughts, including ruminative thoughts of overdosing on them.

At evaluation, Ms. B is casually dressed, pleasant, with fair hygiene and poor eye contact. Her speech is decreased in rate, volume, and tone; mood is "devastated and depressed"; affect is labile and tearful. Her thought process reveals occasional thought blocking and her thought content includes suicidal ideations and paranoid thoughts. Her cognition is intact; insight and judgment are poor. During evaluation, Ms. B reveals a history of alcohol and marijuana use, but reports that she has not used either for the past 15 years. She further states that she had agreed to a trial of medica-

Table 1

Psychiatric and nonpsychiatric adverse effects of interferon

Psychiatric adverse effects
Depression ranging from mild to suicidality
Irritability, aggressive behavior
Worsening mania
Insomnia
Nonpsychiatric adverse effects
Fatigue
Myalgia, fever, flu-like symptoms
Hair loss
Cytopenias

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tion first for her liver disease and had deferred any discussion of liver transplant at the time of her diagnosis with HCV.

Laboratory tests reveal a normal complete blood count, creatinine, and electrolytes. However, liver functions were elevated, including aspartate aminotransferase (AST) of 107 U/L (reference range, 8 to 48 U/L) and alanine aminotransferase of 117 U/L (reference range, 7 to 55 U/L). Although increased, the levels of AST and ALT were slightly less than her levels pre-sofosbuvir–ribavirin trial, indicating some response to the medication.

What is your first step in managing Ms. B's suicidal thoughts and HCV?

a) discontinue sofosbuvir and ribavirin, restart her psychotropic medications
b) continue sofosbuvir and ribavirin, and switch psychotropic medications
c) discontinue sofosbuvir and ribavirin, switch psychotropic medications
d) switch antiviral medications, restart her psychotropic medications

The authors' observations

Approximately 170 million people worldwide suffer from chronic HCV infection, affecting 2.7 to 5.2 million people in the United States, with 350,000 deaths attributed to liver disease caused by HCV.[1]

The standard treatment of HCV genotype 1, which represents 70% of all cases of chronic HCV in the United States, is 12 to 32 weeks of an oral protease inhibitor combined with 24 to 48 weeks of peg-interferon (IFN)–alpha-2a plus ribavirin, with the duration of therapy guided by the on-treatment response and the stage of hepatic fibrosis.[1]

In 2013, the FDA approved sofosbuvir, a direct-acting antiviral drug for chronic HCV. It is a nucleotide analogue HCV NS5B polymerase inhibitor with similar *in vitro* activity against all HCV genotypes.[1] This medication is efficient when used with an antiviral regimen in adults with HCV with liver disease, cirrhosis, HIV coinfection, and hepatocellular carcinoma awaiting liver transplant.[2]

Table 2

Reported adverse effects for HCV treatments: IFN-free vs IFN-containing regimens

Symptoms	IFN-free regimen	IFN-containing regimen
Fatigue	30%	55%
Headache	30%	44%
Insomnia	16%	29%
Nausea	13%	29%
Pruritus	27%	17%
Decreased appetite	6%	18%
Myalgia	9%	16%
Fever	4%	14%
Irritability	10%	16%
Diarrhea	12%	17%
Flu-like symptoms	6%	18%

HCV: hepatitis C virus; IFN: interferon

Combination therapy of peg-IFN-α therapy and ribavirin results in a good sustained viral response, which is defined as an undetectable HCV-RNA level (<50 IU/mL) 24 weeks after treatment withdrawal.[3] Unfortunately, significant neuropsychiatric adverse events often limit its use (***Table 1, page 50***). The most common psychiatric adverse effect is depression, with a prevalence of 30% to 70%, with psychosis, suicidal ideation, and suicide attempts.[3]

TREATMENT Medication restarted

Ms. B is admitted to the psychiatric unit for management of severe depression and suicidal thoughts, and quetiapine, 400 mg at bedtime, fluoxetine, 40 mg/d, and lamotrigine, 150 mg/d, are restarted. The hepatology team is consulted for further evaluation and management of her liver disease.

She receives supportive psychotherapy, art therapy, and group therapy to develop better coping skills for her depression and suicidal

Clinical Point

Psychiatric adverse effects associated with IFN-α therapy in chronic HCV patients are the main cause of antiviral treatment discontinuation

Related Resources

- Rado J. Hepatitis C among the mentally ill: review and treatment update. 2017;16(3):41-47.
- U.S. Department of Veterans Affairs. Interferon and ribavirin treatment side effects. www.hepatitis.va.gov/provider/reviews/treatment-side-effects.asp.
- American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HVC guidance: recommendations for testing, managing, and treating hepatitis C. www.hcvguidelines.org.

Drug Brand Names

Daclatasvir • Daklinza
Fluoxetine • Prozac, Sarafem
Interferon-alpha • Intron A
Lamotrigine • Lamictal
Ledipasvir/sofosbuvir • Harvoni
Ombitasvir-paritaprevir-ritonavir plus dasabuvir • Viekira Pak XR
Quetiapine • Seroquel
Ribavirin • Rebetol

Clinical Point

Be cautious when prescribing sofosbuvir in patients with comorbid psychiatric illness to avoid exacerbating depressive symptoms

thoughts and psychoeducation about her medical and psychiatric illness to understand the importance of treatment adherence for symptom improvement. Over the course of her hospital stay, Ms. B has subjective and objective improvements of her depressive symptoms.

The authors' observations

Psychiatric adverse effects associated with IFN-α therapy in chronic HCV patients are the main cause of antiviral treatment discontinuation, resulting in a decreased rate of sustained viral response.[3] Chronic HCV is a major health burden; therefore there is a need for treatment options that are more efficient, safer, simpler, more convenient, and preferably IFN-free.

Sofosbuvir has met many of these criteria and has been found to be safe and well tolerated when administered alone or with ribavirin. Sofosbuvir represents a major breakthrough in HCV care to achieve cures and prevent IFN-associated morbidity and mortality.[4,5]

A randomized trial reported[5] sofosbuvir–ribavirin was associated with fewer adverse events than peg-IFN–ribavirin. Influenza-like symptoms and neuropsychiatric events were less common among patients receiving sofosbuvir–ribavirin than among those receiving peg-IFN–ribavirin (***Table 2, page 51***). Patients who received 12 weeks of sofosbuvir and ribavirin with peg-IFN had a low rate of treatment discontinuation (2%), compared with previously reported rates among patients receiving IFN-containing regimens for a longer period.

Our case report highlights, however, that significant depressive symptoms may be associated with sofosbuvir. Hepatologists should be cautious when prescribing sofosbuvir in patients with comorbid psychiatric illness to avoid exacerbating depressive symptoms and increasing the risk of suicidality.

What medication would you use to treat HCV?

a) continue combination of sofosbuvir and ribavirin
b) ledipasvir/sofosbuvir
c) daclatasvir and ribavirin
d) ombitasvir-paritaprevir-ritonavir plus dasabuvir

Bottom Line

Interferon (IFN)-based treatment often is not suitable for many patients with hepatitis C virus (HCV) because of comorbid depression and the risk of increased suicidal thoughts. Such patients benefit from treatment with an IFN-free regimen such as sofosbuvir. However, be cautious when prescribing sofosbuvir to patients with existing psychiatric illness to avoid exacerbating depressive symptoms and increasing the risk of suicidality. Robust treatment and monitoring of depression is necessary to limit psychiatric morbidity in HCV treatment.

OUTCOME Refuses treatment

Ms. B is seen by the hepatology team who discuss the best treatment options for HCV, including ledipasvir/sofosbuvir, daclatasvir and ribavirin, and ombitasvir/paritaprevir/ritonavir plus dasabuvir. However, she refuses treatment for HCV stating, "I would rather have no depression with hepatitis C than feel depressed and suicidal while getting treatment for hepatitis C."

Ms. B is discharged with referral to the outpatient psychiatry clinic and hepatology clinic for monitoring her liver function and restarting sofosbuvir and ribavirin for HCV once her mood symptoms improved.

The authors' observations

A robust psychiatric evaluation is required before initiating the previously mentioned antiviral therapy to identify high-risk patients to prevent emergence or exacerbation of new psychiatric symptoms, including depression and mania, when treating with IFN-free or IFN-containing regimens. Collaborative care involving a hepatologist and psychiatrist is necessary for comprehensive monitoring of a patient's psychiatric symptoms and management with medication and psychotherapy. This will limit psychiatric morbidity in patients receiving antiviral treatment with sofosbuvir and ribavirin.

It's imperative to improve medication adherence for patients by adopting strategies, such as:

- identifying factors leading to noncompliance
- establishing a strong rapport with the patients
- providing psychoeducation about the illness, discussing the benefits and risks of medications and the importance of maintenance treatment
- simplifying medication regimen.[6]

More research on medication management of HCV in patients with comorbid psychiatric illness should be encouraged and focused on initiating and monitoring non-IFN treatment regimens for patients with HCV and preexisting bipolar disorder or other mood disorders.

Clinical Point

Collaborative care with a hepatologist is necessary and limits psychiatric morbidity in patients receiving antiviral treatment

References

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