Effect of Ondansetron, a 5-HT_3 Receptor Antagonist, on Fatigue in 2 Veterans With Hepatitis C

To the Editor: Profound fatigue is a clinically significant complication of liver disease. More than 4 million people in the United States (2%) have been infected with the hepatitis C virus (HCV), of whom 2.7 million are chronically infected.[1] Currently, there are 223,000 veterans positive for hepatitis C.[2] Among veterans with chronic hepatitis C, there is an increased number of cases with hepatocellular carcinoma. Meanwhile, there is increasing evidence that HCV infection can affect brain function with symptoms of cognitive dysfunction, disabling fatigue, and quality of life reduction.[3]

The current treatment of chronic hepatitis C patients is interferon and ribavirin combination therapy, which is associated with numerous neuropsychiatric side effects, the most common of which are fatigue, depression, cognitive dysfunction, and anxiety.[4] Currently, there are very few available therapies for fatigue associated with chronic hepatitis C. Recent studies have shown that fatigue and psychomotor slowing may resolve in patients with hepatitis C after treatment with ondansetron,[5] a serotonin antagonist—specifically, a serotonin-3 (5-HT_3) receptor subtype antagonist. This property indicates alteration of serotonergic neurotransmission in HCV-infected patients with chronic fatigue.[6]

The presence of proinflammatory cytokines may influence the response to escitalopram in major depressive disorder. Recently, Eller et al[7] found that a higher level of tumor necrosis factor-alpha (TNF-α) might predict a nonresponse to treatment with escitalopram. They also described that changes in the levels of soluble interleukin-2 receptors (sIL-2R) during the treatment were different in responders and nonresponders. That study indicates that new approaches are needed for the treatment of mental health problems in patients with hepatitis C.

I report the effect of orally administered ondansetron on fatigue and depression in 2 patients with chronic hepatitis C. To evaluate the effect on fatigue, my colleagues and I used the fatigue impact scale[8] modified by using 21 items derived from interviews with multiple sclerosis patients concerning how the fatigue impacts their lives.[9] Each item on the modified fatigue scale could be graded from 0 to 4. In parallel with the fatigue scale, my colleagues and I also used the Beck Depression Inventory-II (BDI-II).[10]

Case 1. Mr A, a 42-year-old man, has chronic hepatitis caused by hepatitis C, genotype 1A. In March 2006 he was diagnosed with mood disorder (*DSM-IV* criteria) due to a general medical condition (hepatitis C), with a major depressive–like episode. Initially, his depression responded to treatment with citalopram, which was gradually increased to 40 mg/d. In July 2007, treatment with peginterferon 150 μg sc every week and ribavirin 600 mg po bid was started for 48 weeks. After 4 weeks, this treatment led to a drop of > 2-log of viral load of hepatitis C copy number (initially log 6.7), and the viral load was undetectable by week 12 of treatment in September 2007. In January 2008, while still treated with peginterferon and ribavirin, he started to experience poor sleep pattern, extreme anxiety, sexual dysfunction, and debilitating fatigue regardless of the ongoing treatment with citalopram. At that time, his score on the modified fatigue impact scale was 72 and his score on the BDI-II was 54. Treatment with ondansetron 4 mg po bid was started. At week 4, his fatigue score was 47 and his depression score was 38; at week 6, the fatigue score was 56 and the depression score 39; and at week 8, the fatigue score was 37 and the depression score was 26. At that time, ondansetron was discontinued.

Case 2. Mr B, a 51-year-old man, has chronic hepatitis C, genotype 1A. In May 2008, he presented with symptoms of worsening depression, and at the time he was drinking 3 or 4 glasses of wine on an almost daily basis. He reported that his depression dated back to 2004 when treatment of HCV with peginterferon and ribavirin was initiated and led to undetectable hepatitis C viral load. In 2004, treatment with different selective serotonin reuptake inhibitors (SSRIs) was initiated (originally paroxetine, followed by sertraline, and currently citalopram 40 mg/d). Despite the treatment with citalopram, his score on the modified fatigue impact scale was 62 and his score on the BDI-II was 50. Treatment with ondansetron 4 mg po bid was started, and his fatigue and depression scores were as follows: on week 2, the fatigue score was 54 and the depression score was 33; on week 4, the fatigue score was 40 and the depression score was 34. At that time, ondansetron was discontinued.

Most of the results regarding fatigue in patients with hepatitis C were published in specialized gastroenterology journals. In my opinion, it is important to make these results available to a wider audience of psychiatrists. In patients with hepatitis C treated with interferon-α, up to 45% develop depression.[4] Interferon-α–induced depression is associated with increases in plasma levels of interleukin-6 (IL-6) and TNF-α, inflammatory mediators commonly elevated in depression.[11] In a recent randomized, double-blind, placebo-controlled study, Piche et al[5] described that ondansetron significantly reduced the fatigue scores with more than 30% improvement on days 15, 30, and 60 ($P < .01$), whereas placebo did not. The observations reported here are in accordance with that study.

Disorders associated with excess inflammation or other immune abnormalities, including diabetes, coronary artery disease, Crohn's disease, rheumatoid arthritis, cancers, HIV infection, and multiple sclerosis, are associated with an increased prevalence of depression. It is interesting that symptoms of post–myocardial infarction depression are characterized by prominent fatigue and irritability rather than depressed mood.

Currently there are no widely used effective therapies for fatigue associated with chronic hepatitis C. The 5-HT_3 antagonist ondansetron in combination with an SSRI had a clinically significant positive effect on fatigue in veterans with hepatitis C.

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doi:10.4088/PCC.08l00755