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A longitudinal study evaluating the effects of interferon-alpha therapy on cognitive and psychiatric function in adults with chronic hepatitis C

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ABSTRACT

Objective: To prospectively evaluate for changes in objective cognitive performance (attention, memory, and executive function) and psychiatric symptom severity (depression, anxiety, fatigue, and pain) in patients before, during and after interferon-alpha based therapy (IFN) for chronic hepatitis C virus infection (HCV).
Methods: 33 HCV+ adults were evaluated two months before IFN initiation (baseline), three months into IFN, and six months following IFN termination (IFN+ Group). 31 HCV+ adults who did not undergo IFN therapy were evaluated at baseline and six months later (IFN− Group). At each evaluation, participants completed the Neuropsychological Assessment Battery (NAB) Attention, Memory and Executive Functions Modules, the Beck Depression Inventory, Second Edition (BDI), Generalized Anxiety Disorder Inventory (GADI), Fatigue Severity Scale (FSS), and Brief Pain Inventory (BPI).
Results: Compared with the IFN− Group, the IFN+ Group experienced significantly ($p < 0.050$) increased symptoms of depression, anxiety, fatigue and pain during IFN therapy relative to baseline. In the IFN+ Group, psychiatric symptoms generally returned to baseline levels following IFN termination. Sustained viral response was associated with significantly lower depression and fatigue. No significant changes in cognitive performance were observed.
Conclusions: During IFN, patients with HCV evidence significantly increased psychiatric symptoms, including symptoms of depression, anxiety, fatigue and pain. These psychiatric symptoms are generally short-term and remit following IFN termination, with increased benefit if viral clearance is achieved. However, IFN is not associated with significant declines in objective cognitive performance during or following IFN.

Introduction

Approximately 2.2% of adults world-wide are chronically infected with the hepatitis C virus (HCV) [1], and approximately 10–15% of these cases progress to advanced liver disease resulting in decompensated liver cirrhosis, hepatocellular carcinoma, liver transplantation, or death [2]. Until recently, standard of care for HCV was combination therapy including both PEGylated interferon-alpha and ribavirin. For HCV genotype 1, combination therapy is typically for 48 weeks, while for genotype 2/3, treatment is typically for 24 weeks. In 2011, the Food and Drug Administration (FDA) approved two protease inhibitors, telaprevir and boceprevir, for the treatment of HCV [3]. Thus, current antiviral therapy for HCV can either entail combination therapy or triple drug therapy with pegylated interferon-alpha, ribavirin, and a protease inhibitor. Following combination therapy, sustained viral response (SVR) (i.e., viral clearance for at least six months following treatment termination) is achieved in approximately 40–50% of those with HCV genotype 1, and 75–80% of those with genotype 2/3 [4]. Recent clinical trials suggest that triple drug therapy significantly increases SVR rates among individuals with HCV genotype 1 to above 65% [5–7].

Interferon-alpha is an endogenous cytokine that can also be administered exogenously for the treatment of malignancies such as malignant

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melanoma as well as chronic viral diseases including hepatitis B and HCV. Interferon-alpha based antiviral therapy for HCV (IFN) is associated with significant side effects, the most commonly reported ones including flu-like symptoms (e.g., fever, chills, myalgia, nausea, fatigue), psychiatric symptoms (e.g., depressed mood, anxiety, irritability, emotional lability, agitation, apathy, anhedonia, anorexia, psychomotor retardation, sleep disturbance, sexual dysfunction) and cognitive complaints [8].

Although cognitive complaints are frequently reported during IFN, relatively few studies have attempted to longitudinally characterize neuropsychological function before, during and after IFN using objective neuropsychological tests. Objective neuropsychological testing is important because people do not typically assess their cognitive skills accurately, and subjective cognitive complaints poorly correlate with objective neuropsychological performance [9]. Perhaps due in part to widely varying methodology, results from available cognitive studies are mixed, showing no clear pattern of whether objective cognitive performance declines during IFN, whether impairments abate following treatment termination, nor which cognitive domains are most sensitive to IFN effects [10–24]. In terms of psychiatric side effects, there is a relatively large literature documenting high rates of psychiatric symptoms during IFN administration but significantly less information regarding the possible persistence of these side effects following IFN termination. A recent community survey of 200 patients treated with IFN for HCV found that 84.5% reported psychiatric side effects during IFN, and 42.5% reported psychiatric side effects that persisted up to six months following IFN termination [25]. IFN induced depression is the most prevalent and well-studied IFN induced psychiatric side effect. The most recent meta-analysis on this topic [26] evaluated 26 prospective observational studies that reported on the incidence of IFN induced major depressive disorder in patients treated for HCV; overall cumulative incidence of depression was 25% following 24 weeks of IFN, and 28% following 48 weeks of IFN. Although the depressive symptoms associated with IFN are generally considered to be transient and remit following termination of therapy [8], a handful of case reports have described worsening depression, and at times increased suicidality, following IFN termination [27–30]. In a case series of five patients treated with IFN, suicide was attempted in four cases after IFN termination and was responsible for two deaths [30]. In another report, two attempted suicides and one successful suicide during or shortly after IFN were described [28]. The rates and time course of other IFN induced psychiatric symptoms have been less rigorously studied. However, an expert panel convened by the European Liver Patient's Organization (ELPA) recently published a consensus statement regarding treatment recommendations for the management of mental health problems among HCV infected patients [31]. Based on their review of the available literature on HCV, IFN, and mental health, this consensus statement reports prevalence rates of IFN induced psychiatric side effects ranging from 30 to 70% for depression, 39–80% for fatigue, 18–45% for sleep disturbances, 16–50% for irritability, 11–45% for anxiety, 0–3.2% for mania, 0–0.6% for psychosis, 3.5–10% for suicidal ideation, and 0–0.2% for suicidal attempts.

In light of the inconsistent findings within the cognitive literature, additional well-designed longitudinal studies are warranted to better characterize the trajectory of potential IFN induced cognitive effects both during IFN and following IFN termination. The present study, therefore, utilizes a comprehensive battery of widely used, well-validated, and adequately normed neuropsychological assessment instruments to prospectively evaluate neuropsychological functioning in patients before, during, and after IFN, and also includes a demographically similar (i.e., age, race/ethnicity, gender, education, baseline estimated IQ) control group of untreated HCV patients to control for possible confounding factors such as practice effects. This study additionally adds to the literature on the psychiatric side effects of IFN by simultaneously including well-validated symptom questionnaires to evaluate the severity and persistence of symptoms of IFN induced depression, anxiety, fatigue and pain.

Methods

Participants

A total of 64 adults were recruited from the Portland, Oregon area and assigned to one of two groups: 1) adults with chronic HCV (>5 years) who were about to initiate IFN (IFN+, n = 33), 2) a control group of adults with chronic HCV (>5 years) who were not planning to initiate IFN (IFN−, n = 31). Participants were recruited from Portland area hepatology clinics through referral by the hepatologists, announcements at hepatology clinic HCV education classes, mailings to patients who had previously participated in HCV research, or study advertisements posted in hepatology clinics and hospitals. *Inclusion Criteria*: 1) Able to provide informed consent, 2) HCV status confirmed by the treating hepatologist, medical record verification, and a detectable HCV viral load based on polymerase chain reaction (PCR) test at the time of study enrollment. *Exclusion Criteria*: 1) History of antiviral therapy or chemotherapy for any purpose. 2) Visual or auditory impairments that would prevent valid neuropsychological test administration. 3) History of a major medical or psychiatric condition, or currently unstable medical or psychiatric condition, that was likely to be associated with severe neurological, cognitive, or immune dysfunction at the time of enrollment or would preclude informed consent or valid testing [e.g., stroke, seizures, brain tumors, Parkinson's disease, neurodegenerative dementia, mental retardation, hepatic encephalopathy, human immunodeficiency virus (HIV), traumatic brain injury with loss of consciousness ≥30 min, schizophrenia, bipolar I disorder]. 3) Within twenty-four hours of testing, use of alcohol, illicit substances, or medications with acute cognitive effects such as sedation or intoxication (e.g., benzodiazepines, opiates, muscle relaxants, psychostimulants, steroids, anticholinergics). 4) Alcohol or drug dependence within the past three months (except nicotine or caffeine), based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria [32], confirmed with the Mini-International Neuropsychiatric Interview (MINI) [33].

Procedures

All research was conducted with permission from the Portland Veterans Affairs Medical Center (PVAMC)'s Institutional Review Board and in accordance with the Helsinki Declaration as revised in 1989. All patients were paid $75 per study visit to complete the following study procedures: clinical interview, comprehensive medical record review, a battery of cognitive assessment measures, a battery of psychiatric questionnaires to assess severity of depression, anxiety, fatigue, and pain, and blood sample collection for standard medical laboratory tests including a liver panel (serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), ammonia, bilirubin, and albumin levels), human immunodeficiency virus (HIV) antibody screening, and HCV testing (HCV antibody, followed by HCV recombinant immunoblot assay, HCV PCR Qualitative, and HCV PCR Quantitative if HCV antibody positive). Blood samples were collected by certified phlebotomists in the PVAMC medical laboratory. All other study procedures were administered by one of eight study personnel (VW, SJ, CE, MK, DK, JA, KB, HO) who were trained and supervised by a clinical neuropsychologist (MH). To ensure accuracy, all cognitive and psychiatric measures were scored and then re-scored by separate study personnel. All study data were entered into a database initially and then double-checked by separate study personnel prior to analyses.

Clinical interviews were conducted using a structured case report form, developed specifically for this study, including prompts to screen patients based on each inclusion criteria, gather relevant demographic data, assess for a full range of current and past Axis I psychiatric and substance use disorders using DSM-IV [32] criteria and the MINI [33], evaluate for history of head injuries, and record a comprehensive list of current and previous medical conditions and medications. Study