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Psychiatric Behavioral Aspects of Comanagement of Hepatitis C Virus and HIV

Jeffrey J. Weiss, PhD and Jack M. Gorman, MD

Abstract

Coinfection with HIV hastens the progression of liver disease in persons with hepatitis C virus (HCV) infection. As mortality directly due to HIV continues to decrease among persons who are HIV-positive, coinfection with HCV has emerged as a leading cause of death. There is increasing attention to the need to actively treat HCV infection in HIV/HCV coinfecting patients. Current HCV treatment with pegylated interferon and ribavirin achieves sustained viral response in up to 40% of coinfecting patients but has numerous neuropsychiatric side effects. Providers are hesitant to begin HCV treatment in the coinfecting population given the high prevalence of existing psychiatric illness, cognitive impairment, and substance use disorders. There is an urgent need for research into the psychiatric and behavioral predictors of HCV treatment adherence and virologic outcome, as well as into the optimal psychiatric management of the neuropsychiatric sequelae of HCV therapy.

Introduction

In the developed world, antiretroviral treatment for HIV infection continues to evolve and become more effective in suppressing HIV. Concomitantly, public health policy and behavioral interventions are promoting increased patient access and adherence to available treatments. It is within this context of the increasingly effective treatment of HIV illness, 25 years after the first cases of AIDS surfaced, that greater attention is being paid to the comorbid medical conditions with which persons who are HIV-positive are living and from which they are now dying.

Given its high prevalence and the increasing liver-related mortality rates in persons who are HIV-positive, hepatitis C virus (HCV) infection is arguably the most important comorbid condition affecting this population. In a US sample, Bica et al. [1] reported that end-stage liver disease had risen to become the leading cause of death in hospitalized patients with HIV. Salmon-Ceron et al. [2] reported that liver disease was the most frequent cause of death (31%) in coinfecting patients in France. In this article, we will review the most recent literature on the psychiatric behavioral aspects of comanagement of patients with both HCV and HIV infection (hereafter referred to as “coinfecting” patients).

The psychiatric behavioral management of coinfection is unique given the independent and potentially synergistic effects of HCV and HIV on the brain and behavior. The psychiatric profile of coinfecting patients is further complicated by the high prevalence of intravenous drug use (IDU) history as well as by the neuropsychiatric side effects of the current treatment for HCV, pegylated interferon and ribavirin (PEG-IFN/RBV).

Prevalence and Incidence of Coinfection

There are approximately 3 million persons living with chronic HCV infection in the United States, 1 million persons living with HIV infection, and an overlapping subset of 300,000 to 400,000 persons who are coinfecting. The percentage of persons with HIV who are coinfecting with HCV varies greatly by risk group, with (former) IDUs having by far the highest rates of coinfection due to shared route of transmission.

Miller et al. [3] found in a Vancouver sample of 479 IDUs age 29 years or younger that of those who were HIV-positive (19%), 87% were coinfecting with HCV. Hall et al. [4] report a baseline prevalence rate of 69% coinfection with HCV in a sample of 249 persons enrolled in the Research and Access to Care for the Homeless (REACH) cohort of HIV-infected marginally housed individuals in San Francisco. Of those with an IDU history the coinfection rate was 79%, whereas it was 21% among those without IDU history. Ten subjects who were not HCV infected at baseline were HCV infected at follow-up (mean follow-up was 29 months) clearly indicating that marginally housed persons who are HIV-positive are at risk for becoming newly coinfecting with HCV. There have also been reports of HIV-infected men who have sex with men without a history of IDU becoming infected with HCV putatively through unsafe sex [5].

HIV Coinfection Hastens Progression of HCV/Liver Disease

HCV patients coinfecting with HIV have a significantly elevated relative risk of severe liver disease as compared with HCV monoinfected patients [6]. Coinfecting patients on antiretroviral therapy have been shown to have higher rates of mortality than HCV patients not infected with HIV [7,8]. The goal of PEG-IFN/RBV treatment is to achieve a sustained virologic response (SVR), defined as an undetectable HCV-RNA titer 6 months after completing treatment. PEG-IFN/RBV achieves SVR in up to 55% of HCV monoinfected patients and in up to 40% of coinfecting patients. The treatment of HCV in coinfecting patients generally lasts longer (48 weeks) than for HCV monoinfected patients (24 weeks), and there are higher rates of treatment side effects and of early treatment discontinuation. There are also higher rates of HCV relapse in coinfecting patients with undetectable HCV-RNA at the end of treatment as compared with HCV monoinfected patients [9]. Given that coinfection with HIV hastens the progression of liver disease, there is increasing attention to the need to actively treat HCV infection in coinfecting patients [10].

Effect of HCV on HIV Progression Equivocal

The evidence is mixed as to whether or not coinfection with HCV has a deleterious effect on HIV treatment progression [11]. There are studies that show more rapid progression to AIDS and death in HIV-positive patients coinfecting with HCV as well as studies that do not find this [12]. A recent study by Braitstein et al. [13••] suggests that the deleterious effect of HCV on survival in persons with HIV found in some studies may be mediated by poorer adherence to antiretroviral therapy in this group. These authors found hepatitis C coinfection to be independently associated with nonadherence to antiretroviral therapy as measured by pharmacy refill data in a population-based cohort of HIV-positive persons in British Columbia.

Higher Prevalence of Psychiatric Illness and Substance Use Disorders in Coinfection

Chronic hepatitis C infection is known to be associated with high rates of neuropsychiatric symptoms (mental and physical tiredness, poor concentration, forgetfulness, depression, sleep problems) [14]. The rate of psychiatric illness in persons who are HIV-positive is higher than

in the general population with prevalence estimates of lifetime psychiatric illness in samples of persons who are HIV-positive ranging from 38% to 88% as compared with 33% for the general population [15].

Within the subset of HIV-positive persons who are coinfectd, the rates of psychiatric illness are even higher than in HIV-positive persons who are not infected with HCV. Goulet et al. [16••] studied the prevalence of mental disorders and alcohol-related complications in all veterans receiving care for HIV during the years 1997 to 2002. Over 25,000 veterans were in care, and 18% were coinfectd. Compared with the HIV-monoinfectd veterans, the coinfectd veterans had significantly higher rates of drug disorders (58% vs 22%), alcohol disorders (56% vs 24%), depression (43% vs 28%), posttraumatic stress disorder (18% vs 8%), bipolar disorder (12% vs 6%), and schizophrenia (13% vs 6%). Given that this sample was 97% male, more research is needed on the psychiatric morbidity in coinfectd women.

Greater Neurocognitive Impairment in Coinfection

HIV infection and HCV infection have been independently associated with a subcortical pattern of neurocognitive deficits in the domains of working memory and information processing speed. Studies have begun to examine the additive effects of coinfection on cognitive functioning. Martin et al. [17] compared performance on a test of executive function in coinfectd, HCV monoinfectd, HIV monoinfectd, and uninfected drug users. Controlling for age, premorbid intelligence, and history of IDU, the coinfectd group was more impaired as compared with both the HIV monoinfectd and the HCV monoinfectd group. Ryan et al. [18] investigated neurocognitive functioning in two groups of advanced HIV-positive patients—those coinfectd with HCV and those not coinfectd with HCV. Coinfectd patients exhibited a significantly greater rate of impairment than HIV-monoinfectd patients on tests of executive functioning and were also more likely to meet criteria for HIV-associated dementia. Although these studies were not able to fully control for stage of liver disease and HCV viral load, the findings do support a theory of additive deleterious effects of HIV and HCV coinfection on cognitive functioning.

Side Effects of HCV Treatment

Interferon- α is a cytokine which interacts with the central opioid, serotonin, dopamine, and glutamate systems. The neuropsychiatric side effects of interferon- α treatment are understood to result from its induction of secondary cytokines, such as interleukin-1 (IL-1), IL-2, IL-6 and tumor necrosis factor α [19] and its interference with specific neurotransmitter systems [20]. The mechanism of interferon-induced cognitive impairment may be related to prefrontal cortical hypometabolism in addition to damage to hippocampal cells [21]. Ribavirin is a purine nucleoside analogue which may also contribute to interferon-induced depression [22].

Treatment with PEG-IFN/RBV is associated with numerous hematologic, physical, and neuropsychiatric side effects. The most commonly occurring hematologic events are anemia, neutropenia, and thrombocytopenia. The physical side effects include flu-like symptoms, such as fatigue, myalgia, arthralgia, fever, headache, depressed appetite, nausea, chills, insomnia, and gastrointestinal distress. The most frequently occurring neuropsychiatric symptoms are depression, anxiety, emotional lability, and irritability. Suicidal ideation can occur in the context of depression caused by interferon and successful suicides have been reported in coinfectd patients on treatment [23,24]. Many of the common side effects of interferon (eg, fatigue, anhedonia, loss of appetite, impaired concentration, and insomnia) overlap with the symptoms of major depression. These multiple side effects dramatically decrease quality of life and often lead to physician-initiated or patient-initiated dose reductions and early treatment

discontinuation. The proper management of treatment side effects can greatly reduce the rates of early treatment discontinuation.

Physician and Patient Barriers to Treatment of HCV in Coinfected Patients

The 2002 *National Institutes of Health (NIH) Consensus Development Conference Statement* [25] recommends that all persons with HIV infection be screened for HCV, and that coinfecting patients with chronic hepatitis C be considered for treatment. Given the neuropsychiatric complications which can result from PEG-IFN/RBV treatment, providers are concerned about beginning treatment with patients who have a history of depression, substance use disorders, and other major psychiatric illnesses; consequently, the percentage of medically eligible coinfecting patients being treated for HCV is still quite low. However, there is now a body of literature which documents that the treatment of HCV infection with PEG-IFN/RBV can be as successful in achieving a SVR in HCV-monoinfected patients with psychiatric histories as in patients without significant psychiatric histories when there is adequate integration of medical and psychiatric services and the patients are given the necessary level of support and psychiatric care during PEG-IFN/RBV treatment [26].

There is inadequate awareness among coinfecting patients of the option to treat HCV infection. Hall et al. [4] found that only 68% of the coinfecting patients in the REACH cohort were aware of the possibility of treatment for HCV, and only 3.8% had previously been treated. Nonwhites were found to be less likely to be tested for HCV and to receive subspecialty referral upon testing HCV positive. Thompson et al. [27•] interviewed the primary care providers of the REACH cohort participants to understand more about how providers are assessing eligibility for HCV treatment in this population. Fifty-two providers taking care of 133 patients were interviewed. These providers deemed 69% of the patients ineligible for HCV treatment. The providers cited an average of 3.2 reasons why each patient was ineligible and the most commonly cited reasons were “poor medication adherence likely” (50%), patient not interested in treatment (49%), depression (44%), and active injection drug users (33%).

Although NIH eliminated active drug use as an absolute contraindication for HCV therapy in 2002 [25], providers are very hesitant to begin HCV therapy for patients who actively use illicit drugs [28]. Providers are very likely to view alcohol abuse, injection drug use, and uncontrolled psychiatric disease, particularly depression with current suicidal risk, as clear contraindications to treating HCV in a coinfecting patient [29••]. The major individual barriers to HCV treatment eligibility (low motivation, active injection drug use, alcohol use, depression) are modifiable. With appropriate treatment, coinfecting persons deemed at first ineligible for HCV therapy can become eligible for therapy [30,31].

Taylor et al. [32] present a case report that illustrates this approach. They describe the treatment of HCV in a coinfecting man with relapsing IDU and bipolar disorder. Treatment of HCV was initiated after 4 years of HIV primary care, psychiatric care and substance use treatment not including opioid replacement. At the time of the case report (31 weeks into treatment), the patient had undetectable HCV viral load and had no adverse events related to mental health status or substance use relapse.

In addition to individual level barriers, there are also structural barriers (poor access to HCV testing, provider inexperience in treating HCV, lack of collaborative relationships across disciplines [HIV primary care, liver specialist, psychiatrist], and inadequate reimbursement for HCV treatment) that prohibit coinfecting patients from accessing treatment for HCV infection. One strategy to reduce the barriers to accessing treatment for HCV has been to colocate HCV treatment services at existing sites of treatment and residential placement of persons who are HIV-positive. Treatment models have been proposed at methadone maintenance treatment

programs [33], prisons [34], and HIV primary care sites [35]. An additional model under development is the adaptation of directly observed therapy programs to treat HCV in coinfecting injection drug users [36].

Treatment of HCV in Coinfected Patients

Four randomized controlled trials of 48 weeks of PEG-IFN/RBV in coinfecting patients were reported on in 2004 [23,37,38,39]. Overall, these studies showed a far superior HCV virologic response to PEG-IFN/RBV as compared to other treatment arms (standard interferon and ribavirin or pegylated interferon alone). The SVRs ranged from 14% to 38% for genotypes 1 and 4 and from 44% to 73% for genotypes 2 and 3. In these trials, 12% to 39% of patients discontinued treatment early. The range of depressive adverse events ranged from 11% to 37%. These results have since led to an increased interest in the treatment of HCV in coinfecting patients in clinical care and PEG-IFN/RBV becoming the standard of care.

Patients with psychiatric illness and substance use disorders were excluded from these clinical trials. No information is provided in the publications of three of these trials [23,37,38] regarding the use of antidepressants to treat interferon-induced depression. In the fourth trial [39], the patients with moderate/severe depression were treated with citalopram; all but one had good clinical response and completed the course of PEG-IFN/RBV treatment. One additional patient discontinued interferon due to a psychotic episode.

Two additional prospective studies from Spain have recently been published on coinfecting patients treated with PEG-IFN/RBV. Santin et al. [40] studied 60 patients, excluding those with active drug use in the past 12 months and/or history of severe psychiatric illness. Only 16 patients (27%) achieved SVR, and 20 patients (33%) discontinued treatment early. Eight of the 60 (13%) patients developed depression, and only one discontinued treatment due to it. Four of the 60 (7%) patients developed psychosis, and three of them discontinued treatment due to this. No information is provided on the treatment of interferon-induced depression or psychosis.

Solà et al. [41] studied 79 coinfecting patients and 78 HCV monoinfected patients treated with PEG-IFN/RBV for 48 weeks. Patients with a history of severe psychiatric conditions, particularly depression, were excluded from the study. The coinfecting and monoinfected patients were matched by sex and age. The monoinfected patients had greater SVR (44% vs 24%). A higher percentage of patient in the coinfecting group (25%) than in the monoinfected group (9%) withdrew or stopped treatment early. No information is provided regarding the use of antidepressant medication prior to or during treatment.

A final study, also from Spain [24], described the neuropsychiatric side effects of 113 coinfecting patients on interferon alpha (nonpegylated) and ribavirin. The study excluded patients with current mood or psychotic disorders, substance abuse during the last year, and history of major depressive disorder. As determined by clinical interview, 40% of the subjects developed symptoms of depression during treatment, most often (60% of cases) in the first 3 months of treatment. Those patients with moderate or severe depression (44%) were treated with citalopram. There was good clinical response in all but one of these patients, who discontinued interferon treatment. In addition, two patients with no prior history of psychosis became psychotic, one patient became delusional requiring hospital admission, and one patient committed suicide during a "psychotic-paranoid breakdown" after 2 months of treatment.

Use of Prophylactic Antidepressants

Musselman et al. [42] showed that in patients with malignant melanoma, pretreatment with paroxetine, a selective serotonin reuptake inhibitor, was effective in reducing depression

caused by interferon-alfa during the first 12 weeks of treatment. This study is often cited as a rationale for starting patients on antidepressants prior to HCV treatment. There have, however, been no randomized, controlled trials in either HCV monoinfected or coinfecting patients to address whether or not the use of preemptive treatment with antidepressants reduces the incidence of depressive side effects during HCV treatment.

Hoffman et al. [43] report a case series of four coinfecting patients with no prior history of psychosis who developed psychosis including paranoia while on PEG-IFN/RBV treatment. The authors posit that coinfecting patients with a history of substance use are at increased risk for the development of psychotic symptoms during PEG-IFN/RBV treatment because of the additional neurotoxic effects of HIV and past liver and brain injury due to substance use. They used mood stabilizing and antipsychotic medications to successfully treat the interferon-induced psychosis. They argue against the use of prophylactic antidepressant medication in the coinfecting patient group given the potential for antidepressants to precipitate mania in vulnerable individuals. Cohen and Alfonso [44] have successfully used a mood stabilizer, rather than an antidepressant, for pretreatment in coinfecting patients with history of substance use beginning on PEG-IFN/RBV.

Psychiatric Evaluation of Coinfecting Patients Beginning HCV Treatment

Given the high rates of psychiatric illness in coinfecting patients as well as the neuropsychiatric side effects of HCV treatment, we recommend thorough psychiatric evaluation of all coinfecting patients prior to initiation of HCV treatment. Patients with diagnosed psychiatric illness who are stably treated should be monitored closely during treatment for the development of clinical depression and/or psychosis. Patients with untreated psychiatric illness or those who are unstable on treatment should be stabilized prior to initiating interferon treatment. Patients with subthreshold psychiatric symptoms are at high risk for the development of clinically significant symptoms during interferon treatment. The option of pretreatment with psychotropic medication should be discussed with these patients, and if pretreatment is not chosen, they should be closely monitored during interferon treatment. Pretreatment with antidepressants is not recommended in coinfecting patients with no psychiatric symptoms. These patients should be closely monitored during treatment for the development of clinically significant symptoms.

Adherence to HCV Therapy

Many coinfecting patients who are eligible for HCV treatment present with numerous risk factors for nonadherence (depression, neurocognitive impairment, current substance use, low self-efficacy). In addition, the neuropsychiatric side effects of HCV treatment place patients at risk for nonadherence. In the HCV literature, nonadherence has been used to refer to physician-initiated interferon dose reductions [45] as well as to early treatment discontinuation [46]. Nonadherence has not been used in the HCV literature as it is frequently used in the HIV literature to refer to missed medication doses by the patient [29••]. No research has been published to date on the rates of adherence (ie, missed doses) to PEG-IFN/RBV treatment or on the relationship between adherence rates and achievement of SVR.

Conclusions

Clinical trials have demonstrated that HCV can be effectively treated in up to 40% of coinfecting patients. However, many barriers remain to treating HCV in coinfecting patients in clinical practice. There is inadequate patient knowledge regarding the risks of hepatitis C coinfection and of the option for treatment. The neuropsychiatric side effects of PEG-IFN/RBV treatment in the coinfecting have been found to be more severe than in HCV monoinfected patients [39], likely due to the neurotoxic effects of HIV and secondary effects on the central nervous system

of some antiretrovirals. Given the high prevalence of psychiatric and substance use disorders and cognitive impairment in the coinfecting population, there is often provider reluctance or refusal to begin HCV treatment. The seven HCV treatment studies which have been published on coinfecting patients [23,24,37–41] exclude patients with severe psychiatric illness or active drug use and, with the exception of the two studies done by Laguno's group [24,39], do not report on how neuropsychiatric symptoms were managed. It would be of great benefit to this evolving literature if the other study teams would publish detailed data on how depression was assessed and treated in these trials and the relevant clinical outcomes. Studies are needed in clinical populations of coinfecting patients to identify psychiatric and behavioral factors which predict HCV treatment adherence, neuropsychiatric side effects, early treatment discontinuation, and sustained viral response. These data are urgently needed to guide patient and provider treatment decision-making as well as to develop effective interventions to increase the rate of success in treating HCV in the coinfecting population.

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