Hepatitis B and C Co-infection with Co-morbid Pyschiatric Illness

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Hepatitis B and C co-infection represents a challenging therapeutic conundrum. Due to the increasing rate of hepatitis C infection in the population, treatment of hepatitis C (often with cirrhosis) in the face of co-morbid psychiatric illness is an increasingly common clinical challenge. Literature on the diagnosis, treatment and public health issues related to hepatitis B and hepatitis C co-infection and their management in major psychiatric illness is reviewed. Practical issues associated with compliance, adverse drug reactions, and the use of growth factors and psychotropic medications to control co-morbid and/or treatment-emergent psychiatric disorders in viral hepatitis are discussed.

INTRODUCTION

Hepatitis B (HBV) and hepatitis C (HCV) are chronic viral infections of the liver which represent a substantial public health burden in the United States (1). The natural history of both infections involves advancing hepatic fibrosis resulting in cirrhosis with the associated complications of hepatocellular carcinoma (HCC), liver failure and need for liver transplantation. Due to an increased incidence of HCV infection, the burden of HCV-related complications is projected to increase in the next decade (2). Psychiatric illness (notably substance abuse) predisposes patients to exposure to HBV and HCV, and psychiatric illness (including cognitive, anxiety, psychosis, and mood disorders) may emerge as medication-related side effects from antiviral treatment for HCV (3–9). As such,

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internists, hepatologists, and psychiatrists treating these patients need to be aware of the co-morbid hepatic and psychiatric illnesses in these patients and to offer care in an integrated model of care delivery.

TREATMENT OF HBV AND HCV

Treatment of HBV or HCV when it occurs as the sole liver disease is, in either case, a long and intensive process involving multiple medications with significant adverse reactions and need for close monitoring while on therapy. Co-infection with both viruses and the therapy of a co-infected patient is a less commonly-encountered clinical situation. Literature in the area of HBV and HCV co-infection is also relatively sparse (10).

Recent advances in the treatment of HCV have resulted in newer and more aggressive therapies (11–13). The burden to society from having a large population with cirrhosis and end-stage liver disease, along with the scarcity of donor organs available for liver transplantation, has driven the need to treat larger numbers of patients, some of whom may have

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been considered ineligible for treatment in the recent past (data from the United Network for Organ Sharing (UNOS)). Examples include patients with cytopenias due to cirrhosis, and patients with a history of severe psychiatric illnesses (e.g. mood, psychotic, and active substance use disorders) (14). Paradoxically, those patients may be the ones most in need of medical therapy for HCV, either as a means to possibly prevent the development of liver cancer or because liver transplantation may not be an option in the presence of ongoing unresolved major psychiatric illness (including substance abuse disorders), which are currently considered contra-indications to liver transplantation.

The impetus to "push the envelope" in the treatment of HCV has resulted in the creation of a patient pool that amplifies the challenges in the treatment of HCV, with special issues—side effect management, compliance and outcome. It has also been suggested that treatment rates for HCV in the community are low and that enhancing the ability of the internist to recognize and treat potentially reversible contraindications to therapy would greatly increase the number of these treatment candidates (15).

COMPLICATIONS OF HBV/HCV

Complications HBV and HCV include cirrhosis, hepatocellular carcinoma (HCC), variceal bleeding, further hepatic decompensation, including ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, malnutrition, and finally, liver failure and death as a result of one or more of these clinical events (16). There is also a risk of acute liver failure from other viral hepatitides (mainly Hepatitis A), should they occur (17).

Chronic HBV is a risk factor for HCC. The risk of HCC in patients with chronic HBV and positivity for HBe antigen is 100-fold greater than in a matched cohort of patients without chronic HBV (18). HCV is also an independent risk factor for the development of HCC, with recent studies showing an increase in incidence in the United States (19). Studies indicate that while HBV and HCV are both independent risk factors for the development of HCC, the greatest risk is experienced by the subgroup of patients co-infected with both viruses (20–23). Smoking is another additive risk for the development of HCC in patients with HCV (24).

Renal dysfunction is also a consequence of advancing liver disease. Its occurrence in decompensated cirrhosis is associated with increased mortality (25). The importance of this parameter is reflected in the incorporation of serum creatinine measurements in the calculation of the MELD (Mortality in End Stage Liver Disease) score, which uses serum bilirubin and INR in addition to predict mortality in patients with end-stage liver disease (26). MELD scoring has been validated across populations and clinical situations—variceal bleeding (27), Transjugular Intrahepatic Portosystemic Shunt (TIPS) (28), transplantation (29)—and is currently used to stratify patients for allocation of organs in the wait list for liver transplantation.

SURVEILLANCE FOR HEPATOCELLULAR CARCINOMA

While surveillance for HCC was previously a matter of controversy, recent evidence supports the use of surveillance for HCC, as lesions detected during surveillance are demonstrated to be smaller and associated with improved survival (30). Smaller lesions or "early HCC" has also been demonstrated to be predictive of better surgical outcome (31). Evidence based medicine may thus be inferred to support the use of six to12 month interval repeated Alpha Feto-protein (AFP) measurements and an imaging study with high sensitivity to detect focal lesions in the liver in cirrhotic patients with the assumption that early intervention will increase survival.

Multiple phase or helical Computed Tomography (CT) with early arterial contrast scans is the most commonly used imaging modality in the United States, but many other techniques have been described (32). Imaging modality of choice at most centers depends on the diagnostic "level of comfort" of the local radiologist and is usually used in concert with AFP estimations. If a lesion is detected, appropriate interventions include a referral for liver transplantation, as well as consideration of other interventional procedures (e.g., hepatic resection, percutaneous ablation, selective angiogram with chemoembolization) (33). Imaging also adds other important information such as the presence/absence of ascites, the patency of the major hepatic blood vessels and bile ducts, the size of the spleen, and the presence or absence of collateral circulation associated with portal

hypertension (e.g., varices, patent umbilical vein, spontaneous porto-systemic shunts).

AFP elevations commonly signal the development of HCC, although a third or more of HCC may present with normal AFP (34), and vice versa, most patients with chronic HBV and HCV may present with mild-to-moderate elevation of AFP in the absence of HCC (35). Despite its limited sensitivity and specificity, both absolute values and serial measurements of AFP are certainly helpful in the differential diagnosis of HCC, as patients with persistently elevated levels are more likely to develop HCC than those with fluctuating levels (36).

VARICEAL BLEEDING, HEPATO-RENAL SYNDROME, AND OTHER COMPLICATIONS

The risk of variceal bleeding can be assessed by upper endoscopy and staging of size and characteristics of varices and other signs of portal hypertension, as mortality from the first episode of variceal bleeding still ranges between 20%–30% (37). If varices are confirmed on endoscopy, prophylactic intervention with endoscopic banding and pharmacologic therapy such as propranolol may be indicated to decrease the risk of gastrointestinal hemorrhage. Screening and prophylaxis has been shown to be associated with low cost and improved quality adjusted life years (38). The risk of further decompensation may be assessed by the use of ultrasound and clinical exam. If ascites is not detected, the risks of renal dysfunction (the hepatorenal syndrome) and of peritonitis are practically nonexistent.

Supportive care and prevention of further decompensation is essential. Fluid retention is managed by the institution of a 2 gm/day sodium restricted diet. Patients are counseled that this is best achieved by reading labels on all foods ingested to calculate the total sodium intake for the day, merely decreasing the addition of salt to food at the table will not suffice. Aldactone is the diuretic of choice in the face of fluid overload despite such sodium restriction. Most hepatologists would consider a dose of 100 mg a day as the starting point, to be increased in increments of 50–100 mg/day to a maximal dose of 400–600 mg/day. Small doses of furosemide may be added for additive benefit. Therapy is limited only by the development of hyperkalemia or renal dysfunction (39).

Adjunctive measures to protect renal function include the avoidance of all nephrotoxic drugs, including non-steroidal anti-inflammatory medications (40). In the absence of ongoing heavy alcohol use acetaminophen in doses of up to 3 grams/day may be used safely as an alternative to non-steroidal anti-inflammatory agents (41).

While malnutrition is not an independent predictor of poor outcome in this population, it is associated with worsening of liver disease (42). Low protein intake has been demonstrated to result in worse encephalopathy and clinical outcome, contrary to previously held beliefs (43). This has led to guidelines which support the use of daily protein intake of 1–1.5 g/kg body weight in these individuals (44). Protein from vegetable and fish sources has been considered superior to that from other sources. Overwhelming evidence suggests that the use of lactulose, neomycin and zinc in a step-wise fashion is the method of choice for control of hepatic encephalopathy, and that protein restriction leading to further malnutrition should not be recommended (45).

Vaccination for hepatitis A (HAV) is recommended for all patients with chronic HBV and /or HCV. This recommendation is based on the increased mortality and morbidity associated with acute or fulminant hepatic failure from HAV infection in patients with chronic HBV and/or HCV as compared with the general population (46). Seroconversion rates with vaccination approach those of the general population in cirrhotics who have compensated disease, while are lower with decompensated liver disease (47). Vaccination for influenza and pneumococcus is also recommended (48,49).

MANAGEMENT OF HCV/HBV CO-INFECTION

In co-infected patients, considerations must be given as to which virus to treat first. Data on the natural history or progression of disease in patients co-infected with HBV and HCV is sparse. Available data indicate that co-infection does predispose to higher transaminase levels, increased parenchymal inflammatory changes and a faster progression of fibrosis to cirrhosis (51,52). Viral dynamics in co-infection with HBV and HCVviruses is also not well characterized. Some data suggest that HCV infection can suppress viral

replication in HBV, leading to a persistent HBc antibody positivity, with an absence of HBs antigen or antibody (52–54). Others have suggested that serologically silent HBV infection may be responsible for poor response rates to HCV therapy (55,56).

Most clinicians make decisions on treatment and temporal sequence of treatment on a case-by-case basis. The virus that is considered to be the predominant pathogen in liver damage is typically the one that is treated first. If no predominant pathogen is identified one may consider first initiating treatment for HBV. Two reasons support this consideration: 1) the theoretical concern that treatment and clearance of HCV could cause a flare of HBV, due to data that HCV suppresses HBV replication in a co-infected state (52–54). 2) clearance of HBV would increase the response rate to interferon therapy for HCV, since HBV has been shown to impair treatment response of HCV to interferon (55,56). Furthermore, treating the patient with lamivudine, adefovir, or entacavir first, which are oral drugs that are usually well tolerated, would allow providers to assess the stability of the patients mental status, compliance to therapy and control of schizophrenia prior to initiating interferon based therapy.

THE PATIENT WITH HBV, HCV, CIRRHOSIS, AND MAJOR PSYCHIATRIC ILLNESS

There are several issues to consider when co-infected patients have the co-morbidities of cirrhosis, pancytopenia and major psychiatric illness. Cirrhosis had historically been considered a relative contraindication to antiviral therapy for HCV due to concerns with decompensation of liver disease due to interferon. Compensated cirrhotics have, however, been treated in large numbers in clinical trials involving use of both interferon and pegylated interferon. Safety data from these trials assures us that those patients with cirrhosis who have no evidence of decompensation such as the presence of ascites, encephalopathy or severe coagulopathy may safely undergo interferon-based antiviral therapy (57). Patients who have a history of decompensated liver disease, whose complications are stable on treatment, are also considered for antiviral treatment as long as they are followed closely and (possibly) starting antivirals at low doses (58).

Limiting factors in initiating treatment also include cytopenias (leucopenia, thrombocytopenia or even pancytopenia), which are related to the presence of splenomegaly from portal hypertension. Commonly accepted cutoffs for treatment include a pre-treatment platelet count of 50,000/mm^3 or more, normal white count and normal hematocrit. Bone marrow stimulating agents such as granulocyte-monocyte colony stimulating factor (filgrastim) and erythropoetin are used during treatment with interferon to counter the bone marrow suppression that results from the use of interferon (59,60). The best response rates to therapy in clinical trials are observed in patients who take at least 80% of their doses and for at least 80% of the study duration (61), leading to the conclusion that growth factor support must be tried prior to dose-adjustment in the interest of improved viral clearance rates.

Severe untreated psychiatric illness has long been considered a contraindication to antiviral treatment (4). Untreated psychiatric disorders are associated with reduced compliance and thus decreased response to therapy (62). In addition, interferon is known to exacerbate pre-morbid depression and psychosis and may induce new episodes of depression or psychosis, sometimes with fatal outcomes (due to suicidal behavior) in HCV patients treated with IFN (63–65). However, increased psychiatric symptoms following IFN have not been uniformly found, suggesting that the previous concern about IFN treatment for patients with pre-existing psychiatric illness may be excessive (66,67). Interestingly, endogenous interferon profiles have been reported to be disordered in patients with schizophrenia and two small clinical studies have been published evaluating interferon therapy for schizophrenia. No evidence of exacerbation of schizophrenia was found in these studies, which used doses similar to the ones used for therapy of HCV (68,69).

DISCUSSION

Management of HCV with IFN in a patient with a major psychiatric illness (such as mood, psychotic, anxiety, cognitive, and/or substance use disorders) adds a level of complexity to an already challenging treatment model. Clearly, such patients are at risk for behavioral decompensation following major psy-

chosocial stressors, such as life-threatening complications of hepatitis. The implications for treatment of hepatitis vary according to the psychiatric illness. Depressed patients may have cognitive distortions and or/or poor cognitive function due to untreated mood states, which interfere with understanding of their illness and resulting in poor compliance. Depressed patients may also exhibit apathy and hopelessness, which lead to poor motivation for self care. In severe depression, there is always a risk of suicidal behavior.

Patients with psychotic disorders may have unremitting hallucinations and/or delusions, which may interfere with cognitive processing of stimuli and understanding of verbal instructions regarding their medical illnesses, and may exhibit poor judgment in self care In addition, psychotic patients with paranoid delusions regarding medications may believe that medications prescribed for their HCV are "poison" or otherwise threatening and thus may be noncompliant.

Anxiety disorder patients may be increasingly anxious in the context of the threat to bodily integrity represented by hepatitis; this increased anxiety interferes with the processing of stimuli and results in poor understanding of medical advice. In addition, sleeplessness and fatigue from un-resolved anxiety states may exacerbate fatigue from the liver disease.

Severe liver disease may result in cognitive impairment; in some cases this cognitive impairment may be additive with cognitive impairment from pre-existing substance use disorders. Cognitively impaired patients have greater difficulty with understating instructions, compliance, and are likely to have more problems completing substance use treatment.

Continued substance abuse in HBV/HCV patients may result in decreased cognitive function, increased risk for mood, psychotic, and anxiety symptoms, and lead to poorer compliance, repeated exposure to HBV/HCV through high-risk behavior, and increased risk of complications of intoxication and withdrawal states.

All of these factors may make patient compliance with complex drug regimens for HBV/HCV especially problematic. In addition, internists, hepatologists and their staff members may be relatively inexperienced with dealing with the subtleties of behavioral decompensation in patients with severe psychiatric illness. However, chronic psychiatric patients (particularly

those with co-morbid substance abuse/dependence) are at higher risk for exposure to HBV/HCV and are thus in need of treatment. With close monitoring and appropriate psychiatric intervention, treatment for hepatitis C can be safely performed in this population with success rates that are comparable to the general population.

Optimum treatment of these patients involves close collaborative relationships among the internist, hepatologist and the psychiatrist. Communication between these physicians for patient monitoring is crucial. As all antipsychotic, antidepressant, and mood stabilizing medications (except lithium carbonate) are hepatically metabolized, dose adjustments of psychotropic medications to accommodate decreased hepatic function are commonly necessary. Patients with substance use disorders should be routinely referred for 12-step recovery programs (e.g., Alcoholics Anonymous or Narcotics Anonymous); more impaired substance dependence patients may be considered for inpatient substance dependence treatment models.

As patients may experience mood and/or psychotic symptoms referable to IFN/RBV, surveillance for these symptoms during antiviral therapy is similarly essential. It is necessary for internists to recognize these issues involved in the treatment of these special populations and be aware of the risks and benefits of therapy for HCV in this setting so they may accurately refer, counsel and support these patients. Routine psychiatric consultation prior to and periodically throughout antiviral therapy with IFN may assist in the identification of psychiatric complications, including the possibility of IFN-associated suicidal ideation (3,70). Aggressive management of mood and psychotic disorders in hepatitis patients is essential. Patients should be counseled and prepared to self-monitor for mood and psychotic symptoms as part of their self-management paradigm of antiviral treatment. Antidepressant medications can be considered prophylactically for IFN-associated mood symptoms, and can be continued until IFN therapy is completed (3,8). Among antidepressant classes, the SSRIs, SNRIs, mirtazepine, and bupropion can be considered (71). For IFN-associated mania or psychosis, mood stabilizers or antipsychotic agents can be used, although cautious monitoring of hepatic function and serum medication levels should be done with valproate and carbamazepine therapy (3,72).

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HBV/HCV patients with co-morbid major psychiatric illness represent a singular challenge for internists, hepatologists, and psychiatrists. A comprehensive inter-specialty treatment model is desirable for these patients. HBV/HCV patients with adequate social support and comprehensive biopsychosocial treatment would be expected to be more able to remain compliant with treatment and thus have a chance at better clinical outcomes for these chronic illnesses. ∎

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