Special management challenges in hepatitis C

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ABSTRACT

Infection with hepatitis C virus (HCV) often coexists with other conditions and patient factors that complicate its management. Infection with HIV is a particularly widespread and vexing comorbidity of HCV infection, since HIV facilitates HCV transmission and renders HCV more opportunistic. This review provides a practical overview of major comorbidities and patient factors that require special management considerations in patients with HCV infection.

In and of itself, infection with hepatitis C virus (HCV) poses a challenge to the clinician, both for the scope of the pathology it can cause and for the management it requires. Yet its management is more daunting when we consider that HCV infection often coexists with other comorbidities, adding further complexity to clinical decision-making. This article reviews considerations surrounding coinfection with human immunodeficiency virus (HIV) and other major factors that demand special attention when managing patients with HCV infection.

I. Coinfection with HIV

Coinfection with HIV and HCV has become widespread: approximately 25% to 30% of all HIV-positive patients in the United States, or about 200,000 to 300,000 persons, are also infected with HCV.[1] The frequency of coinfection varies among subgroups of patients: it is as low as 4% to 10% in HIV-positive men who have sex with men, as high as 50% to 90% in HIV-positive injection-drug users, and 98% in HIV-positive hemophiliacs.[2–4]

These figures, although high, may underestimate the true frequency of coinfection, since 4% of coinfected patients have been reported to have a negative HCV antibody test despite documented HCV viremia.[5] Therefore, when HCV coinfection is highly suspected, a negative antibody test should not rule out infection and should be complemented with HCV RNA testing by polymerase chain reaction (PCR).[6]

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HIV ENHANCES HCV TRANSMISSION

HIV appears to facilitate both the sexual and the vertical (mother-to-infant) transmission of HCV.

Among sexually active homosexual men, HCV infection is three times as frequent in those who are HIV-positive as in those who are HIV-negative.[7,8] Similarly, several studies show a consistently higher rate of vertical transmission of HCV among mothers infected with both HIV and HCV as compared with mothers infected with HCV only.[9–12] In one study, HIV coinfection in the mother imparted an odds ratio of 3.76 (95% confidence interval [CI], 1.89 to 7.41) for transmission of HCV to the infant.[11] In another study, the rate of vertical HCV transmission was 18.2% among mothers infected with both HIV and HCV compared with 6.4% among those infected with HCV alone.[12] Many other variables can modulate this risk of vertical transmission in individual patients, including HCV viral load and the mode of delivery.[11]

HOW THE VIRUSES AFFECT EACH OTHER

Before the era of highly active antiretroviral therapy (HAART) for HIV infection, AIDS-related conditions accounted for most deaths in HIV-infected patients. In contrast, end-stage liver disease is now emerging as a major cause of morbidity and mortality in this population. A recent report from one major US medical center indicated that end-stage liver disease was the cause of death in 50% of the center's HIV-positive patients in 1999, up from just 11.5% in 1991; 90% of these HIV-positive patients who died from liver disease in 1999 were positive for HCV.[13]

HIV makes HCV opportunistic

In the setting of HIV infection, HCV behaves more aggressively, with higher rates of replication and high-

er degrees of liver damage. This manifests as follows:

Lower rates of infection clearance. Spontaneous clearance of HCV occurs in up to 15% to 30% of patients who are not coinfected with HIV,[14] compared with only 5% to 10% of those who are coinfected.[15]

Higher rates of viral replication. Patients with HIV coinfection seem to have higher HCV RNA levels than their counterparts without HIV.[16] In one study of HCV-infected injection-drug users,[17] those who were also infected with HIV had a significantly higher HCV viral load than those who were not (7.19 log vs 6.73 log; $P < .001$).

More frequent progression to cirrhosis. Several studies suggest that patients with HIV–HCV coinfection progress to cirrhosis significantly sooner than those with HCV infection alone, even after adjusting for alcohol consumption. In a study from Spain,[18] the mean estimated interval from HCV infection to cirrhosis was 7 years in patients coinfected with HIV vs 23 years in those infected with HCV alone. Also, the degree of $CD4^+$ cell deficiency has been linked with an increased risk of progression to liver fibrosis: patients with $CD4^+$ cell counts less than 500 cells/mL were 3.2 times more likely (95% CI, 1.1 to 9.2) to have advanced fibrosis on liver biopsy than were patients with a better-conserved immune system.[19]

Earlier development of hepatocellular carcinoma. A recent report from Spain[20] found that hepatocellular carcinoma occurred at a younger age (mean 42 years vs 69 years) and after a shorter interval of HCV infection (mean 18 years vs 28 years) in HIV-coinfected patients than in those without HIV.

HCV's effect on HIV is more equivocal

Whether HCV behaves as a cofactor for HIV progression is controversial. In the Swiss HIV Cohort Study,[21] which included 1,157 patients coinfected with HIV and HCV, the presence of HCV was independently associated with progression to an AIDS-defining condition or death (hazard ratio of 1.7 [95% CI, 1.26 to 2.30]). HCV also was associated with less robust $CD4^+$ cell recovery after HAART, but it did not predict HIV virologic response to HAART. Daar et al[22] showed that increases in HCV viral load are associated with progression of HIV disease: for every 1-log increase in HCV RNA, there was a 1.66 relative risk (95% CI, 1.1 to 2.51) for progression to AIDS.

In contrast, Sulkowski et al[23] found no difference in the risk of developing AIDS-defining conditions, the risk of death, or the increase in $CD4^+$ cell count during HAART between 873 HIV/HCV-coinfected patients and 1,082 patients with HIV infection alone.

Some have speculated that HIV–HCV coinfection may reflect poorer adherence to medication regimens, since it is often a marker for injection-drug use.[6]

HAART and HCV: Do they mix?

It also is controversial whether HAART changes the progression of HCV-associated liver disease. Some have suggested that there may be an immune reconstitution phenomenon whereby the liver inflammatory pattern could worsen upon the start of HAART and improvement in the patient's cellular immune function. One study reported a transient increase in HCV viral load, in aminotransferase levels, and in mean score on the Knodell histology index (from 8 to 13) after the start of HAART.[24] Other studies found HAART to have no impact on HCV replication,[25,26] and another indicated that HAART had a protective effect on progression of liver fibrosis.[27]

All antiretroviral drugs have been implicated in some degree of liver toxicity. However, HCV infection is well established as an independent risk factor for the development and increased severity of liver toxicity in patients starting or receiving HAART. Sulkowski et al[28] reported a 12% incidence of severe hepatic damage among 211 HIV-infected patients receiving protease inhibitor–based HAART regimens, and HCV infection was a strong predictor of its occurrence. Martinez et al[29] reported a 9.7% incidence of severe hepatotoxicity among 610 HIV-infected patients receiving nevirapine-based HAART; 51% of the study population was also infected with HCV, and hepatotoxicity was predicted by the cumulative time on antiretroviral drugs and by HCV infection.

■ MANAGING COINFECTED PATIENTS

Assessing for HCV. Guidelines from the US Public Health Service and the Infectious Diseases Society of America recommend that every HIV-infected person be tested for HCV infection by enzyme immunoassay. However, up to 4% of patients who are truly coinfected with HIV and HCV may have a false-negative result for HCV by enzyme immunoassay.[5] Therefore, when risk factors are present, or if there is an unexplained elevation of liver function test values, HCV viral load should be assessed by reverse transcriptase PCR. Once the presence of replicating HCV has been established, further characterization and staging should be strongly considered, following the general principles outlined earlier in this supplement.

When to treat HCV infection. Soriano et al[30] found that a $CD4^+$ cell count greater than 500

cells/mL in patients with HIV–HCV coinfection is associated with an increased likelihood of HCV virologic response to interferon alfa ("interferon" hereafter). Patients with counts above 350 cells/mL (or > 300 cells/mL with HIV viral load under control) are generally considered eligible for HCV therapy.

Ideally, treatment of hepatitis C in patients with HIV–HCV coinfection would precede the initiation of HAART, since patients would have more conserved immune function, less risk of opportunistic infections, and no added toxicity or interactions between drug regimens. However, most patients with coinfection are already on HAART when HCV infection is discovered. As long as awareness about drug interactions, added side effects, and medication adherence is kept high, concurrent treatment of the two viruses is not contraindicated. Patients with low $CD4^+$ cell counts should probably delay HCV treatment until HAART has resulted in a better immune status.[31]

Patients with HIV–HCV coinfection are candidates for HCV therapy if they have any of the following:[31]

- HCV genotype 2 or 3
- HCV genotype 1 and elevated alanine aminotransferase levels
- Normal alanine aminotransferase levels and a biopsy with any degree of fibrosis.

The timing of therapy depends on the clinical factors outlined above.

Treatment success rates. The largest series of patients with HIV–HCV coinfection to date (N = 111) showed a 28% end-of-treatment HCV response rate with the combination of interferon and oral ribavirin.[32] Overall estimates of the end-of-treatment and sustained virologic response rates for this combination in patients with HIV–HCV coinfection are 35% and 25%, respectively.[31]

As detailed earlier in this supplement, the combination of peginterferon alfa ("peginterferon" hereafter) and ribavirin has become the regimen of choice for treating HCV infection. The use of this combination in patients with HIV–HCV coinfection has so far been addressed only in preliminary reports. The French RIBAVIC investigators[33] reported a 44% virologic response rate at the end of 48 weeks of treatment among 110 coinfected patients receiving peginterferon and ribavirin. Chung et al[34] reported a 53% combined virologic and histologic response rate at 24 weeks of therapy among coinfected patients receiving peginterferon and ribavirin.

To put these numbers in perspective, the overall end-of-treatment and sustained virologic response rates are usually reported to be about 10% higher in patients infected with HCV alone.

Side effects to watch for. Treatment with interferon is challenging, as patients usually feel fatigued and typically lose weight (10 kg, on average). Patients taking interferon or peginterferon usually have reductions in hemoglobin and white blood cells and in the absolute number (but usually not the percentage) of $CD4^+$ cells.[35] In a study of 20 patients with HIV–HCV coinfection who were treated with interferon and ribavirin, the mean $CD4^+$ cell count fell from 350 to 284 cells/mL at 6 months, with no change in the percentage of $CD4^+$ cells.[36]

Drug interactions. Interactions between ribavirin and several common components of HAART regimens should be a paramount consideration when planning for HCV therapy. Ribavirin inhibits the phosphorylation of pyrimidine analogs (zidovudine, zalcitabine, and stavudine) to the active triphosphate form.[37] This effect has not been shown to translate to clinical failure of either ribavirin or the pyrimidine analogs,[38] although there is an additive effect of ribavirin and zidovudine on the incidence of anemia.

Ribavirin increases the conversion of didanosine to its active metabolite, and concurrent use of these two drugs may increase the risk of pancreatitis.[35] Moreover, ribavirin may inhibit mitochondrial DNA polymerase, and it has been reported to raise the incidence of HAART-related mitochondrial toxicity.[39]

II. Other challenges and difficult-to-treat groups

Other patient factors and comorbidities confer added risks for HCV infection or complicate patient management. These include immunosuppression (eg, due to solid-organ transplantation, diseases requiring immunosuppressive therapy, or chronic renal failure requiring hemodialysis), various extrahepatic or autoimmune manifestations, and membership in certain high-risk demographic groups. Because many patients with these and other special factors have been excluded from large efficacy trials of hepatitis C therapies,[40] controlled studies in these patients are needed. In the meantime, management of HCV-infected patients with these factors should be informed by the special considerations reviewed below.

■ PSYCHIATRIC DISORDERS: Risk factor for infection, frequent side effect of therapy

Risk-seeking behaviors among people with a psychiatric diagnosis make this population vulnerable to

increased rates of HIV and HCV infection. Rosenberg et al[41] reported an HCV prevalence of 19.6% among 931 patients with severe mental illness, which is 11-fold higher than that in the general US population.

The presence of a psychiatric or substance-abuse diagnosis in an HCV-infected patient poses a great challenge, since interferon or peginterferon may exacerbate or precipitate mental illness. Depression occurs in 16% to 29% of interferon-treated patients, anxiety or emotional lability in 3% to 34%, and insomnia in 18% to 24%.[42] Irritability, nervousness, fatigue, and impaired concentration are also common. The most concerning, though rare, reported events include suicide, suicidal or homicidal ideation, and relapse into drug addiction or drug overdose.

Although several reports suggest that patients with psychopathologic symptoms before starting interferon therapy may have more severe adverse psychiatric effects in response to treatment,[43,44] other groups believe that patients with a psychiatric diagnosis can successfully complete interferon therapy.[45–47] Some argue that withholding therapy from members of a stigmatized class "raises questions about fairness and discrimination."[48] The use of interferon or peginterferon therapy in psychiatric patients should be coupled with heightened awareness, closer follow-up, and more thorough probing for psychological disturbance.

■ RENAL DISEASE: Optimal HCV therapy unclear

HCV has a well-described association with mixed cryoglobulinemia and a variety of renal lesions, of which the most prominent is membranoproliferative glomerulonephritis.[49] Although severe nephrotic syndrome and rapidly progressive glomerulonephritis often require steroids, cytotoxic agents, or plasmapheresis for their management, milder forms of renal involvement respond to antiviral treatment alone.[50] The optimal therapeutic algorithm and the role of peginterferon in this setting still need to be established by carefully designed clinical trials.

■ RENAL FAILURE: Dialysis carries high infection risk, restricts treatment options

HCV infection is common in patients undergoing hemodialysis. Antibodies to HCV were found in 9.3% of patients participating in the 1997 National Surveillance of Dialysis Associated Diseases in the United States.[51] Additionally, because of the diffuse immune dysfunction associated with end-stage renal disease (ESRD), up to 3% of serologic tests for HCV in ESRD patients are reported to be false-negative.[52] PCR testing for HCV RNA has shown that the prevalence of HCV infection among dialysis patients can be as high as 20% to 30%.[51]

Because there is a risk for significant liver disease and because cirrhosis is a contraindication to kidney transplantation, liver biopsy should be performed early in dialysis patients who test positive for HCV RNA, to assess the histologic impact of the liver disease.[53] Combined liver–kidney transplantation may be considered in selected dialysis patients with cirrhosis.[53]

The mainstay of HCV therapy for ESRD patients has been interferon. It is usually given at a dosage of 3 MU subcutaneously three times a week after each hemodialysis session, for 6 to 12 months. Sustained virologic response rates have ranged from 15% to 64% in dialysis patients treated before kidney transplantation and followed for up to 19 months.[54,55] Reduced clearance of interferon in ESRD patients seems to account for the increased side effects and reduced tolerability in these patients, but it also accounts for greater efficacy than would be expected with interferon monotherapy in other patients. Peginterferon's role in patients with ESRD needs to be established in controlled trials.

Use of ribavirin in patients with chronic renal failure is associated with accumulation in erythrocytes and a profound and lasting hemolytic anemia. Although ribavirin's package insert lists creatinine clearance lower than 50 mL/min as a contraindication to its use, Bruchfeld et al[56] reported a pilot study of interferon–ribavirin combination therapy in 6 HCV-infected patients undergoing dialysis. Reduced ribavirin doses were used (mean of 170 to 300 mg/day), plasma levels were monitored, and patients were closely followed for development of anemia. Four of the 6 patients had end-of-treatment response, but only 1 had sustained virologic response at 10 months.

■ KIDNEY TRANSPLANT: Little role for interferon

Liver failure from chronic hepatitis C is a leading cause of death among long-term survivors of kidney transplantation.[57] Studies that have used interferon for treatment of HCV infection in renal transplant recipients have included small numbers of patients and have shown low rates of SVR (~ 10%).[58] Moreover, the use of interferon in this setting has raised concern over the precipitation of acute rejection, acute renal failure, and graft dysfunction (reported at incidences of 15.4% to 63.6% in various series[52]). Therefore, use

of interferon is relatively contraindicated in kidney transplant recipients; if considered, it should be reserved for experts or the setting of clinical trials.

Transplant can be successful in HCV-infected patients. In some series, liver transplant recipients with HCV infection have been able to undergo kidney transplantation with a reasonable degree of success. Kidney transplantation should be offered for ESRD after liver transplantation, even in the presence of HCV infection, to patients with stable liver function and no signs of liver failure.[59]

Studies assessing the impact of kidney transplantation on survival in HCV-positive patients with ESRD have shown that patients who received a kidney transplant had better survival than their counterparts who were awaiting transplantation.[60]

■ LIVER TRANSPLANT: Risk of recurrent HCV remains

Worldwide, HCV infection remains the main indication for orthotopic liver transplantation (OLT). In patients with demonstrable HCV viremia before transplantation, reinfection of the graft occurs almost universally. HCV-induced damage shows an accelerated course thereafter, so that graft cirrhosis develops in 20% to 30% of patients at 5 years.[61]

Several factors have been identified as markers for severe HCV recurrence after OLT,[62] including:

- High pretransplant or early post-transplant levels of HCV
- HCV genotype 1b
- Coinfection with cytomegalovirus
- The number of rejection episodes (probably as a marker of cumulative immunosuppressive load).

Several strategies have been advocated for treating HCV recurrence following OLT: preemptive treatment before transplant, early post-transplant therapy, or targeted therapy once recurrence is established. Studies of interferon and ribavirin have shown end-of-treatment response rates of about 30% and sustained virologic response rates of about 20%.[63,64] However, increased rates of side effects, primarily severe anemia, have been observed, so that ribavirin dose modification (based on renal function) is recommended.[65]

So far, the use of peginterferon has been reported in the setting of retreatment for HCV-infected OLT recipients who are nonresponders to interferon and ribavirin. Smallwood et al[66] reported sustained virologic response in 3 of 15 patients (20%) in this setting. Clearly, further studies are needed to assess the value of peginterferon as initial therapy for recurrent HCV infection in OLT recipients.

■ PREGNANCY: Ribavirin demands its exclusion

The teratogenic effects of ribavirin are of utmost concern in female patients of childbearing age. HCV-infected women who take regimens that include ribavirin must absolutely assure that they avoid pregnancy during treatment and for 6 months after completing treatment. Treatment of HCV can always be deferred until after pregnancy.

At the same time, mother-to-infant transmission of HCV can be a concern, especially in women with HIV–HCV coinfection. As detailed above, vertical transmission of HCV is increased threefold when an HCV-infected woman is also infected with HIV.[12] Additionally, in one study vertical transmission of HIV occurred more often in mothers who were coinfected with HCV than in mothers with HIV alone.[67]

■ AFRICAN AMERICANS: More likely to be infected, less responsive to therapy

HCV infection poses special problems in African Americans, whose infection rate (2.5% to 3.5%) is twofold to threefold higher than that of the general US population.[68] An estimated 22% of HCV-infected Americans are African American.[69]

The prevalence of HCV genotype 1 in African Americans is as high as 95%. In an early study of consensus interferon monotherapy, the sustained virologic response rate in African Americans was 2%, or one sixth the rate of all patients treated.[70] This lower response rate was confirmed in a reanalysis of five large trials of interferon monotherapy.[71] Adding ribavirin to interferon increases the response rate but has shown a variable effect on sustained virologic response among African Americans. A recent study of combination therapy with interferon and ribavirin among 99 US veterans (42 of them African American) found sustained virologic response in 18% of white patients (and in 26% of those who completed therapy) but in none of the African Americans.[72]

Response rates to peginterferon and ribavirin among African Americans are difficult to discern from published studies. In one study,[73] univariate analysis suggested that white vs nonwhite status predicted response to treatment, but this is not the same comparison as African Americans vs "other." However, multivariate analysis of the same study found that white vs nonwhite status did not predict response. Only 5% of the 1,121 patients in this series were African American.[73]

The observed lower treatment response rates in African Americans may have multiple causes. Iron in the liver may impede response to antiviral therapy. African Americans with HCV infection are 5.4 times as likely as whites to have increased ferritin or transferritin saturation levels.[74] Even more important, the viral dynamics of HCV appear markedly different between African Americans and whites. It is well known that viral kinetics in response to interferon follows a two-phase dynamic. Within 24 to 48 hours after initiation of interferon monotherapy there is a very rapid (0.5- to 2.0-log) decline in viral counts. This is followed by a much slower further decline in viral counts over many months. The first-phase decline in viral counts is 0.8 log lower in African Americans than in whites. The second phase also reveals slower viral elimination.[75] Others have noted that in African Americans the vigorous CD4-proliferative response to HCV infection was not accompanied by the expected increased production of gamma interferon, suggesting a dysfunctional CD4 response to HCV in African Americans.[76]

Treatment recommendations for the HCV-infected African American patient are difficult at this time. Clearly, those who are eligible should be considered for controlled clinical trials. Otherwise, treatment needs to be individualized. We recommend antiviral therapy with pegylated interferon and ribavirin for African Americans with HCV genotype 2 or 3. For those with genotype 1, the decision should be made by the patient, armed with the best data available. More African Americans clearly need to be included in studies of newer therapeutic strategies.

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