

ADVANCES IN HCV

Current Developments in the Management of Hepatitis C Virus Infection

Hepatitis C Virus Infection in Special Populations



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G&H What do we mean by special population groups in relation to patients infected with hepatitis C virus?

SF Special population groups are patient groups that have not been well served in relation to currently available therapies. For example, there are groups of patients that do not respond well to the currently available, standard-of-care regimens, such as pegylated interferon (PEG-IFN) α , ribavirin, and protease inhibitors (PIs). Such populations include African American patients and cirrhotic patients. Then, there are special patient populations in whom current medical regimens are contraindicated. In some patients, such as patients with HIV and hepatitis C virus (HCV) coinfection and posttransplant patients, PIs are contraindicated. PEG-IFN α is contraindicated in patients who have active or a history of substantial psychiatric disease or have a history of autoimmune disease. Ribavirin is contraindicated, for example, in patients with renal failure who are on dialysis or patients with anemia. This situation complicates treatment because the studies that we base many of our treatment decisions on do not typically include these special populations, and, therefore, we do not have adequate information about them.

G&H Which special populations with HCV infection in America are the most challenging or require the most attention?

SF All the groups just mentioned are challenging in different ways. Every group presents very difficult, unique challenges that need to be overcome. The important ones, at

least in terms of numbers of patients, are African Americans and cirrhotics. African Americans have the highest prevalence of HCV infection among any racial or ethnic group in the United States. Although they are eligible to receive the currently available regimens, they do not respond as well to treatment as other patient groups. As for cirrhotic patients, they also are eligible for current medical regimens but also respond less well than noncirrhotic patients. Cirrhotic patients are the ones most in need of effective treatment because they are potentially the sickest of all. They are closest to needing liver transplantation and to development of hepatocellular carcinoma.

G&H What do office-based physicians need to keep in mind regarding racial disparities and HCV infection?

SF As far as screening goes, the screening recommendations for African Americans and non-African Americans are the same. We currently have a 2-pronged screening recommendation system. The old strategy was a risk-factor-based model in which primary care physicians, in their history taking, identified risk factors for HCV transmission. If a risk factor was identified, then a diagnostic test for HCV infection was obtained.

This screening protocol has not been very successful. It is suspected that at least half of persons who have HCV infection in the United States are unaware of their infection. Consequently, the US Centers for Disease Control and Prevention recently recommended birth cohort screening in addition to the risk-factor-based model. According to the new recommendation, everyone born

between the years 1945 and 1965 should have a 1-time HCV screening test. This screening recommendation not only applies to African Americans but anyone presenting to a primary care physician or another healthcare provider on the frontlines of medical care, such as gastroenterologists who order screening colonoscopies for patients in the at-risk birth cohort.

Management is no different in the African American population than the non-African American population. We counsel patients that the expected sustained virologic response (SVR) rate for certain special populations is lower than what is reported in published trials. Aside from informing patients about their prognosis when they start therapy, there is not much difference between treating HCV-infected patients who are African American and those of other races or ethnic groups.

G&H What special considerations need to be addressed for patients who are coinfecting with HIV and HCV?

SF When PEG-IFN α and ribavirin were used to treat genotype 1 HCV infection, HIV-infected patients were eligible for therapy, but SVR rates for these patients were, for reasons that are unclear, significantly lower than rates for non-HIV-infected patients with HCV infection. When telaprevir (Incivek, Vertex) and boceprevir (Victrelis, Merck) became available, clinicians expected that these agents would increase the SVR rate in the HIV/HCV-coinfecting population. Unfortunately, these 2 PIs have significant, common drug-drug interactions with the PIs typically used for management of HIV infection. Therefore, clinicians cannot routinely use telaprevir and boceprevir in the HIV/HCV-coinfecting population, and telaprevir and boceprevir are not approved for use in the coinfecting population because of concerns about drug-drug interactions.

Although the findings have not led to any label changes, studies have been performed that show high efficacy and good safety of telaprevir and boceprevir in combination with specific PIs for HIV infection when administered with close monitoring. This information has led some clinicians to treat HIV/HCV-coinfecting patients off-label with specific PI combinations that have been shown to be safe, but the vast majority of coinfecting patients are not being treated for HCV infection, creating a significant unmet medical need. With the availability of highly effective and well-tolerated HIV medications, the leading cause of death in patients with HIV/HCV coinfection is complications related to HCV infection. The need for safe and effective therapy in coinfecting patients will hopefully be addressed by some of the emerging therapies for HCV infection.

G&H How should vertical transmission of HCV be addressed?

SF Fortunately, the risk of vertical transmission of HCV from an affected mother to infant is very low in the United States. Most studies suggest that the rate of transmission is 5% or less. Also, if HCV infection does occur in an infant, the progression of HCV is so slow that it is quite uncommon for complications of HCV infection to appear even into early adulthood. That said, it would be wonderful to devise an effective strategy to prevent vertical transmission of HCV. As recently reported in a literature review by Cottrell and colleagues in the *Annals of Internal Medicine*, no strategy has yet been identified that is effective in preventing vertical transmission of HCV. The current protocol is to advise a woman who is planning for pregnancy or is already pregnant of the slight risk of vertical transmission of HCV. The woman and her partner are told that little can be done to prevent vertical HCV infection, that it is rare, and that if it does occur, symptoms do not typically appear in childhood. Of course, the most effective way to prevent vertical transmission will be curing HCV infection in a woman before pregnancy occurs.

The topic of treatment in this case then goes back to the importance of screening. Patients who are pregnant or are actively trying to become pregnant cannot take antiviral therapy for HCV infection because, for one, ribavirin is teratogenic and, thus, absolutely contraindicated in pregnancy. PIs also are not recommended in pregnancy. If a clinician is going to treat a woman of childbearing potential for HCV infection, it must be carried out when the woman is using effective birth control so that pregnancy is avoided. It would be ideal to have an effective, well-tolerated regimen that could be used over a short period of time for women who wish to become pregnant. Fortunately, with the explosion of research in HCV therapy, such a regimen may be available in the near future.

G&H How are patients with recurrent HCV infection who have undergone liver transplantation prepared for their prognosis?

SF HCV infection is currently the leading indication for liver transplantation in the United States and has been for quite a number of years. Although the group affected is not that large, transplantation patients undergo a very expensive lifesaving procedure and are on very expensive antirejection and antimicrobial medications. The leading cause of death in patients who undergo liver transplantation for HCV, however, is recurrent HCV infection, so when patients undergo evaluation for liver transplantation, they are informed of the risk of severe recurrent HCV infection posttransplant.

In the past, it was observed that the SVR rates with PEG-IFN α plus ribavirin were lower in patients after liver transplantation than in nontransplant patients with HCV infection. Also, when the PIs for HCV infection became available, there was great hope that posttransplant patients with HCV infection would have a higher response rate than they did before and that the problem of recurrent HCV infection after transplant would be diminished. Similar drug-drug interactions to those occurring in patients coinfecting with HIV and HCV, discussed earlier, were observed, however. The PIs interact with the antirejection medications (calcineurin inhibitors) that are used after transplant. Therefore, the current PI regimens for genotype 1 HCV infection are not approved in the posttransplant population. Studies have shown that PIs can be safely used in specific circumstances with very aggressive monitoring; however, because of concerns of drug-drug interactions and the possibility of immunosuppression toxicity, most post-transplant patients have not been treated with the new PIs, and so, this group represents another unmet medical need. Again, the hope is that the emerging therapies for HCV infection will meet this need.

G&H What is an efficient protocol for patients with HCV infection and decompensated cirrhosis?

SF First, the definition of compensated and decompensated cirrhosis should be explained. Compensated cirrhosis is relatively common in cirrhotic patients; they have advanced HCV-associated liver disease, but complications have yet to develop. The 3 most common complications of cirrhosis are esophagogastric variceal bleeding, ascites, and hepatic encephalopathy. Once any 1 of these occurs, the patient now has decompensated cirrhosis. Mortality over the short term for these patients is relatively high. These patients also respond poorly and are intolerant of antiviral therapy for HCV infection. In fact, most patients are not treated with the current medical regimen if they have decompensated cirrhosis for these reasons. They are more vulnerable to adverse events that aggravate disease symptomatology and end-stage liver disease. These patients also are waiting for effective and safe new therapies.

G&H With the range of new anti-HCV agents that are expected to become available, how will HCV infection in special populations be impacted?

SF This is a complicated question. I have been treating liver disease and HCV infection for 18 years, and

I am involved in the majority of the clinical trials of therapies for HCV infection. Still, in my mind, the results reported in current studies with IFN-free regimens are utterly remarkable. The regimens are short, all oral, often pangenotypic, and extremely well tolerated. In addition, efficacy rates often exceed 90%. This is an absolutely revolutionary development in medicine. That said, these new IFN-free regimens have either not been tested at all or tested in small numbers in many of the special populations we have been discussing. In the case of African Americans and cirrhotic patients, a relatively small number of patients have been assessed. At this time, we do not know the impact that the emerging therapeutic regimens will have on these special populations. The majority of experts, however, believe that the various special populations with HCV infection will respond and tolerate IFN-free regimens extremely well and that such regimens should be available within the next year or so.

Studies performed in the years after the approval of these medications (phase 4 trials) will better clarify the safety and efficacy profiles in specific populations, but I suspect that high SVR rates will be observed. The main issue forthcoming will not be safety and efficacy of antiviral regimens, but rather insurance coverage of these expensive medications. This may impact special populations in particular because they are often disadvantaged and often the most in need of effective and safe therapies. It will be unfortunate if access to these medications is limited because of expense and insurance coverage issues.

Dr Flamm has served on the speakers bureau of Vertex and Gilead and the advisory boards of Vertex, Gilead, AbbVie, Bristol-Myers Squibb, and Janssen; acted as a consultant for Merck, Vertex, Gilead, AbbVie, Bristol-Myers Squibb, and Janssen; and received research funding from Merck, Vertex, Gilead, AbbVie, Bristol-Myers Squibb, Boehringer-Ingelheim, and Janssen.

Suggested Reading

Cottrell EB, Chou R, Wasson N, Rahman B, Guise JM. Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2013;158(2):109-113.

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