Nonresponders to Previous Chronic Hepatitis C Treatment

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Opinion statement

The main strategy governing treatment of chronic hepatitis C is the prevention of future liver complications. There is good evidence that curing hepatitis C infection prevents progression of liver disease and allows histologic regression to occur. Therefore, the primary goal of medical treatment is to cure the viral infection. Combination therapy with peginterferon alfa and ribavirin is the current standard of care; there are no other medical therapies currently available. Those who failed to respond to an earlier version of antiviral therapy should strongly consider treatment with peginterferon/ribavirin if possible. Nearly half of patients who start peginterferon/ribavirin are unable to achieve a sustained disappearance of infection. If there were problems related to dosing or adherence the first time around, it is reasonable to consider re-treating with more aggressive support. Nonresponders to the current therapy who have early-stage liver disease can afford to wait until new antiviral agents come along in the next 5 to 10 years. However, physicians should encourage nonresponding patients with advanced fibrosis to consider experimental alternatives in the meantime, provided there is a logical rationale for the treatment proposed. Some re-treatment strategies still aim to cure the hepatitis C virus infection whereas others focus on limiting liver damage. The best candidates for the first strategy are patients who had temporary clearance of the virus during previous treatment and those with hepatitis C virus genotype 2 or 3 infection. Logical candidates for the second strategy are those who already have advanced fibrosis. It is preferable to pursue further attempts at treatment within the framework of a controlled trial. Studies with strong rationales include those investigating high-dose peginterferon/ribavirin, long-term peginterferon suppression, potential immune modulators, and potential inhibitors of liver fibrosis. The rationales are weaker for re-treatment with a second brand of peginterferon/ribavirin, daily standard interferon plus ribavirin, and ribavirin monotherapy.

Introduction

In the past decade, we have seen stepwise improvements in the treatment of chronic hepatitis C virus (HCV) infection. Among patients starting peginterferon/ribavirin combination therapy, a sustained disappearance of HCV infection is now achieved in 40% to 45% of those infected with HCV genotype 1 and approximately 80% of those infected with genotype 2 or 3 [1,2••]. Overall, this represents a five- to 10-fold improvement in response rates over the first interferon regimens used. However, nearly half of patients who start our best available treatment are still not cured, and many others have either contraindications to treatment or insufficient access to health care. Clearly, better treatments and methods of delivery are needed.

Most individuals with chronic HCV infection are asymptomatic, so the main rationale for treating HCV infection is the prevention of liver complications. There is good evidence that curing hepatitis C infection prevents progression of liver fibrosis [3••], and it may improve life expectancy [4]. Therefore, the first goal of treatment—"Plan A"—is to cure the infection. Several trials of experimental therapy for initial nonresponders
have retained curing the infection as the main objective. Studies either use higher doses of peginterferon or ribavirin, or add a third agent. However, even patients who fail to achieve a permanent loss of HCV infection may experience a temporary reversal of liver inflammation and fibrosis while on an interferon-based regimen [5]. This observation has spurred trials of peginterferon long-term, suppressive therapy among virologic nonresponders, as well as pilot studies of potential inhibitors of fibrosis. This “Plan B” accepts the fact that HCV infection cannot be cured in a large number of patients and focuses on either suppressing the infection or limiting the liver damage. It remains to be seen whether or not the coming generation of HCV-specific antivirals will fit into Plan A or Plan B.

Not all nonresponders to antiviral treatment are the same. Some achieve clearance of detectable viremia during the period of treatment and then relapse with reappearance of HCV RNA in the blood after treatment is stopped. Technically, these individuals are not truly “nonresponders,” but “relapsers.” These patients would seem to be the best candidates for further efforts to cure HCV infection, perhaps with modifications of existing treatment. Some truly nonresponding patients may show a decrease in the level of HCV RNA during treatment, but a decrease that is insufficient to accomplish a sustained loss of infection. These patients do not have at least a 99% reduction in HCV RNA by the twelfth week of treatment [6]. Other nonresponders are those who have little or no reduction in the level of virus on treatment. Patients in this group have little chance of responding to further interferon-based treatments and are logical targets for new treatments.

One reason that some patients failed previous antiviral treatment is that they were under dosed. With regard to peginterferon/ribavirin treatment, retrospective analysis of data from a major trial showed that there was a direct relationship between the dose of ribavirin received per kg of body weight and the probability of a sustained virologic response [1]. Peginterferon/ribavirin nonresponders who received less than 10 to 11 mg/kg of ribavirin daily during the previous treatment might be re-treated using 12 to 15 mg/kg of ribavirin daily, with adjuvant epoetin alfa, if necessary, to mitigate the ribavirin-induced anemia.

Another reason for lack of sustained response during previous treatment is poor adherence to the intended therapy. Because of the adverse effects of interferons and ribavirin, many patients discontinue treatment prematurely. If patients with HCV genotype 1 infection—representing over 90% of nonresponders—are able to take at least 80% of their dose of medication for at least 80% of the intended treatment period, the chance of cure increases by 30% [7]. Thus, if there were problems related to dosing, adequate treatment of adverse effects, optimal support, or access to health staff, it is reasonable to consider treating again. This would be particularly true if other favorable treatment-response variables are present, such as infection with HCV genotype 2 or 3, disappearance of viremia during prior treatment, or low viral load, or if the patient is not African-American [8•].

Motivation to pursue experimental approaches should be proportional to the likelihood of progressive liver disease. Multiple studies of the natural history of HCV infection have shown that the factors that are independently associated with the risk of future liver fibrosis are heavy alcohol consumption, male gender, older age at the time of HCV infection, longer duration of infection, persistent elevation of serum aminotransferases, greater degrees of fibrosis and fat in the liver biopsy, and non-African-American ethnicity [9].

### Treatment

#### Diet and lifestyle

- There is no evidence that a specific diet affects the liver in hepatitis C. However, insofar as hepatic steatosis may be fibrogenic, patients should maintain lean body weight and monitor blood sugar.
- Alcohol consumption should be minimized. It is reasonable to suggest no more than one drink per day for those with minimal fibrosis and complete abstinence for those with more advanced fibrosis (septal fibrosis or cirrhosis).
- Taking vitamin E (400 to 800 IU) daily may lower liver enzymes level among patients with hepatitis C, but there is no evidence of long-term benefit.
- Milk thistle may lower liver enzyme levels and is available over the counter in various supplements of uncertain potency. Controlled trials are pending, but no data are available.
- Nonresponders to older antiviral therapies should consider treatment with peginterferon plus ribavirin, if possible.