

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Treatment Strategies for Nonresponders to Hepatitis C Antiviral Therapy

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G&H What are the mechanisms resulting in failure of response to standard therapy for hepatitis C?

JM Nonresponders to standard pegylated interferon (PEG IFN)/ribavirin therapy for hepatitis C virus (HCV) represent a heterogeneous group of patients and the reasons for their failure of response are also heterogeneous or multifactorial. Some patients experience a true lack of response to our current drugs. Others may be unable to tolerate the drugs, thus leading to dose reductions or diminished adherence to the treatment regimen. In summary, there are treatment-related factors, host-related factors, viral factors, and ethnic factors that can all individually contribute to a lack of response.

G&H What ethnic groups are characterized by a lower rate of response?

JM Response to therapy among African Americans is less than half the rate of that seen in non-Hispanic Whites, when matched for genotype and other factors known to affect response. There is also emerging data that among Hispanics in the United States, response is lower when compared to non-Hispanic Whites, though this is not as well documented. The reasons for the lower response rates in African Americans are currently unclear but they are the basis of a large, collaborative and cooperative National Institutes of Health-funded research project, VIRALHEP-C, which is still ongoing.

G&H How does HCV genotype affect response to therapy?

JM Genotype-1-infected patients, who comprise about 70% of all infected individuals in the United States, have the lowest rate of response to standard therapy. Response rates in genotype-1 patients are just under 50%, as compared to patients infected with genotypes 2 or 3. It was initially thought that this discrepancy could be attributed to differences in the so-called interferon-sensitivity-determining regions in the genome that were originally described in Japan. However, these findings have not proved reproducible in other, Western centers. The reasons for lack of response or lower response based on genotype thus remain unclear.

G&H What other conditions are associated with lack of response?

JM Patients coinfecting with HIV have poorer response rates, particularly those infected with genotype 1. Those with advanced liver disease also have lower response rates as do those who are treated for recurrent HCV post liver transplantation. In addition, patients on dialysis for kidney failure are intolerant of ribavirin and are generally difficult to treat, with lower response to interferon monotherapy. All of these conditions are typically associated with poorer treatment tolerance, requiring dose reductions and adjuvant growth-factor therapy more often, and resulting in lower rates of response.

G&H Are there ways to screen HCV patients for potential nonresponse before starting therapy?

JM There are no accurate tests to screen for antiviral nonresponse prior to initiating therapy. There are certain characteristics that can be applied to populations, suggesting a lower likelihood of response. However, none of these are definitive to rule out treatment on an individual, per-patient basis.

These factors include age, with younger patients generally more likely to respond; the proximity of HCV infection, with recently infected patients attaining higher rates of response than those who have been infected for

decades; and gender, as women are more likely to respond than men. Patients with genotypes 2 or 3 and those with low viral load are more likely to respond. Patients who weigh less and have a lower body mass index and those who do not have steatosis or fat accumulation in their hepatocytes also respond better. In addition, patients with greater degrees of liver fibrosis are also less likely to respond. As stated above, none of these factors, alone or in combination, are compelling enough to deny therapy on an individual, case-by-case basis. They can only provide a guide in terms of the likelihood of response.

G&H How do you decide which patients to re-treat with PEG IFN/ribavirin after an initial failure of response?

JM The decision to re-treat depends on the reasons for lack of initial response. Some patients have undergone an inadequate initial course of treatment. They may have reduced their drug doses too early or been prescribed lower doses of ribavirin. In addition, some patients may not have been told to avoid alcohol during the first course of therapy, a factor also associated with nonresponsiveness to therapy. These factors are all correctable with patient education and re-treatment. If these problems are excluded, the severity of the patient's liver disease and other viral and host factors should be examined to provide a sense of the likelihood of response to re-treatment.

G&H How do courses of re-treatment differ from initial therapy?

JM Once the decision to re-treat is made, there are various options. Patients can be re-treated with the optimal therapy that they may not have received during the first course, as described above. Nonresponders can also be treated with a different, more aggressive regimen. They can be treated for longer periods, or with higher doses. The recently completed RENEW study, led by Dr. John Gross of the Mayo Clinic, Rochester, suggests that doubling the dose of PEG IFN, particularly in African American nonresponders, may increase their response rate. Preliminary reports suggest that this regimen is tolerated about as well as standard regimens, but more data from larger trials are needed to confirm the safety and tolerability of this strategy.

For patients in the early stages of liver disease who have had an adequate course of therapy but didn't respond virologically, waiting and watching may be the best course. However, patients with more advanced liver disease have a sense of urgency and would be best suited by some form of intervention. One approach is low-dose maintenance therapy with PEG IFN. There are three large trials currently evaluating this strategy to see if it is effective in

halting the progression of disease while patients await new forms of therapy: the US government-sponsored HALT-C trial, the EPIC (3) trial, and COPILOT. All of these studies are evaluating hundreds of patients with advanced fibrosis to see if receiving low-dose maintenance interferon, without ribavirin, will halt the progression of their liver disease. The rationale for these experiments comes from animal models and earlier clinical re-treatment studies that have shown that interferon has some potential inherent antifibrotic properties. Two-year interim data from COPILOT suggest some benefit but this is only a preliminary finding.

G&H Are any novel drugs available or in research for these patients?

JM Consensus interferon is an alternate interferon molecule developed by scanning interferon alfa subtypes. The large, randomized DIRECT study is currently ongoing to examine the efficacy of consensus interferon in combination with ribavirin for HCV nonresponders. Some data from single centers, which have not studied the drug in a randomized fashion, suggest that it might have a benefit in nonresponder patients. However, further randomized multicenter trials are needed to carefully evaluate this strategy. There is also ongoing work examining the addition of novel drugs to standard combination therapy. Specific polymerase and protease inhibitors are being studied to see if they, in combination with PEG IFN and ribavirin, can convert nonresponders into sustained-response patients. This is currently a very active area of clinical research.

G&H What practice measures need to be stressed in order to achieve the highest rate of response with initial treatment?

JM Adherence to therapy is clearly associated with response. If a patient does not take at least 80% of their medicine, they are less likely to achieve sustained response. However, if a patient is educated before commencing therapy about the importance of adherence as well as receiving information about the potential side effects of treatment, they are much less likely to have problems with tolerance and compliance. I feel that this period of up-front education, before starting antiviral therapy, is very important.

Frequent monitoring during therapy and relative ease of access to the practitioner and their staff in order to deal with patient questions and side effects as they arise are also important in achieving success. If a clinician writes a prescription and tells the patient to come back in 3 months, it is almost certain that therapy will not be successfully completed, yet we still see these types of patients.

Monitoring patients through laboratory tests, including complete blood count, as well as observing for the onset of depression, can be very important. If patients experience depression early, they can be started on an antidepressant, rather than waiting until they develop significant depression and are required to stop therapy. Practitioners, through careful monitoring of hemoglobin levels, can also avoid decreasing the dose of ribavirin by starting growth-factor therapy with erythropoietin. All of these strategies during treatment are very important, not just in nonresponders but in any HCV patient considering antiviral therapy.

Suggested Reading

Bacon BR, McHutchison JG. Treatment issues with chronic hepatitis C: special populations and pharmacy strategies. *Am J Manag Care.* 2005;11(10 Suppl):S296-S306.

Gross JB et al. Double-dose peginterferon alfa-2b with weight-based ribavirin improves response for interferon/ribavirin non-responders with hepatitis C: final results of RENEW. Presented at the 56th annual meeting of the American Association for the Study of Liver Diseases. November 11-15, 2005. San Francisco, CA. Abstract 60.

Lee WM, Dienstag JL, Lindsay KL, et al. Evolution of the HALT-C Trial: pegylated interferon as maintenance therapy for chronic hepatitis C in previous interferon nonresponders. *Controlled Clinical Trials.* 2004;25:472-492.

Poynard T, Schiff E, Terg R, et al. Sustained Virologic Response (SVR) In the EPIC(3) Trial: Week Twelve Virology Predicts SVR in Previous Interferon/Ribavirin Treatment Failures Receiving PegIntron/Rebetol (PR) Weight Based Dosing (WBD). Oral presentation from the 40th Annual Meeting of the European Association for the Study of Liver (EASL). Paris, France. April 14-17, 2005.

Afdhal N et al. (for the COPILOT Trial). Colchicine versus Peg-Intron Long Term (COPILOT) Trial: interim analysis of clinical outcomes at year 2. Presented at the 55th annual meeting of the American Association for the Study of Liver Diseases. October 29-November 2, 2004. Boston, MA. Abstract 171.