

Hepatitis C

Treatment of Acute and Early Hepatitis C

In the March 1, 2009 *Clinical Infectious Diseases*, G. Matthews and colleagues reported findings from the Australian Trial in Acute Hepatitis C (ATAHC), looking at the natural history and treatment of acute and early chronic HCV infection. The analysis included 103 participants – 76 HIV negative and 27 HIV positive – who had a first positive HCV antibody test within six months prior to enrollment and either clinical hepatitis diagnosed within the past year or documented HCV antibody seroconversion within the past two years.

Since the early 2000s, clinicians in several European cities have reported outbreaks of apparently sexually transmitted acute hepatitis C, mostly among HIV positive gay and bisexual men. HIV positive people receiving antiretroviral therapy typically receive regular liver

function tests, which can reveal asymptomatic early HCV infection, but HIV negative people usually are not screened for HCV. Just over half (56%) of the HIV positive participants in this study – but only 8% of the HIV negative individuals – had HCV infection attributed to sexual transmission. Compared with HIV negative participants, the HIV positive patients were older on average, more likely to have HCV genotype 1, and more likely to have high HCV viral load.

Participants started treatment a median of 30 months after the estimated time of HCV infection (six months is considered the cut-off for acute infection) using pegylated interferon plus ribavirin for 24 weeks. (The standard duration of treatment for chronic hepatitis C is 24 weeks for HCV genotype 2 or 3 and 48 weeks for genotype 1, though 48 weeks is recommended for HIV positive indi-

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viduals regardless of genotype.)

Overall, 44% of patients experienced rapid virological response (RVR), or undetectable HCV viral load at week 4 of therapy. Response rates improved with further treatment: 95% achieved early virological response (EVR) at week 12, 90% had undetectable HCV RNA at week 24 (end of treatment response), and 80% achieved sustained virological response (SVR), or continued undetectable HCV RNA at 24 weeks after completion of treatment. The researchers noted that significant differences in response were observed between HIV positive and HIV negative individuals – with the HIV positive patients less likely to clear HCV RNA at the various time points – but nevertheless concluded that, "Treatment responses among HIV-infected individuals with both acute and early chronic infection are encouraging and support regular HCV screening of high-risk individuals and early treatment for recently acquired HCV infection."

Nitazoxanide for Chronic Hepatitis C

Nitazoxanide (Alinia) is an anti-infective agent with activity against a variety of protozoa, bacteria, and viruses; nitazoxanide and its active metabolite, tizoxanide, have been shown to potentially inhibit HCV replication in laboratory studies. In the

March 2009 *Gastroenterology*, a research team led by J.-F. Rossignol from the Romark Institute described results from STEALTH-C1, a study of nitazoxanide prior to pegylated interferon/ribavirin in previously untreated genotype 4 chronic hepatitis C patients in Egypt. Forty participants were randomly assigned to receive the standard-of-care regimen of pegylated interferon alfa-2a (Pegasys) plus 1000-1200 mg/day weight-adjusted ribavirin for 48 weeks, 28 patients received 500 mg twice-daily nitazoxanide monotherapy for 12 weeks followed by a dual combination of nitazoxanide plus Pegasys (without ribavirin) for 36 more weeks, and 28 received nitazoxanide monotherapy for 12 weeks followed by a triple combination of nitazoxanide, Pegasys, and ribavirin for 36 weeks.

Participants receiving the triple combination were significantly more likely than those taking the standard-of-care regimen to achieve RVR at week 4 (64% vs. 38%, respectively) and SVR at week 24 after completion of therapy (79% vs. 50%, respectively). Patients who received the nitazoxanide/Pegasys dual combination regimen had intermediate RVR (54%) and SVR (61%) rates. Adverse events were similar across the treatment arms except for a lower incidence of anemia in the group that did not receive ribavirin.

At the 2008 American Association for the Study of Liver Diseases (AASLD) meeting last October, the Romark researchers presented data showing that the nitazoxanide triple combination regimen also improved response rates compared with standard therapy in patients with HCV genotypes other than 4. At the annual Asian Pacific Association for the Study of the Liver (APASL) conference in February, the company announced promising pharmacokinetic and clinical data from studies of a controlled release nitazoxanide tablet that may enable less frequent dosing.

Predictors of Sustained Response

In order to avoid additional futile treatment of patients who are responding poorly to interferon-based therapy, researchers have studied various factors that may help predict sustained response during early treatment. As reported in the April 2009 *Journal of Clinical Gastroenterology*, J.A. de Segadas-Soares and colleagues from Brazil assessed whether RVR is a positive predictive factor for SVR in various types of genotype 1 chronic hepatitis C patients. The researchers evaluated a total of 167 participants in three categories – treatment-naïve (62%), relapsers during or after previous treatment (13%),

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and prior nonresponders (25%) – who were treated with pegylated interferon alfa-2b (PegIntron) plus ribavirin.

SVR rates were 44% for previously untreated patients, 68% for prior relapsers, and 12% for prior nonresponders. Overall, about one-third of participants (31%) experienced RVR, and these individuals were significantly more likely to achieve SVR (75%) than patients without RVR (23%). RVR also predicted sustained response in each of the three subgroups. Among treatment-naïve patients, 71% who experienced RVR and 29% without RVR went on to achieve SVR. The corresponding SVR rates were 92% with RVR vs. 40% without SVR among prior relapsers, and 50% vs. 8%, respectively, among prior nonresponders. In a logistic regression analysis, RVR and absence of cirrhosis were independent predictors of SVR, leading the investigators to conclude that, "Assessment of RVR is very useful in all pretreatment status patients in predicting SVR and provides information for individualizing therapy."

Treatment Duration for Coinfected Patients

As noted above, the standard of care for treatment of chronic hepatitis C in HCV mono-infected individuals is pegylated interferon plus ribavirin for 24

weeks for people with genotype 2 or 3 and 48 weeks for those with genotype 1 or 4, but guidelines recommend that HIV/HCV coinfecting patients should be treated for 48 weeks regardless of genotype. Prior research in HCV mono-infected people has shown that those who experience RVR may be able to safely shorten the duration of treatment, while slow responders may benefit from prolonged therapy. In a pilot study described in the April 15, 2009 *Clinical Infectious Diseases*, E. van den Eynde and colleagues from Spain assessed whether treatment duration for HIV/HCV coinfecting patients could be similarly tailored based on early response.

A total of 60 coinfecting patients, most of whom were receiving combination antiretroviral therapy for HIV, started treatment with PegIntron plus 800-1400 mg/day weight-adjusted ribavirin, and duration was individualized according to response at weeks 4 and 12. Patients who achieved RVR (HCV RNA < 50 IU/mL) at week 4 completed 24 weeks of therapy, those without RVR at week 4 but complete EVR (defined as HCV RNA < 600 IU/mL) at week 12 were treated for 48 weeks, and those with partial EVR (HCV RNA decrease of at least 2 logs but \geq 600 IU/mL) and undetectable HCV viral load at week 24 were treated for 60 weeks.

Overall, about one-third of patients experienced RVR (16% with genotype 1, 9% with genotype 4, and 58% with genotype 3) and just over half achieved SVR (44%, 27%, and 79%, respectively). Among the 19 participants who experienced RVR, all but two (89%) achieved sustained HCV clearance after 24 weeks of treatment; the rate was highest among genotype 3 patients with low pretreatment HCV viral load. However, almost half (46%) of genotype 1 or 4 patients who did not achieve undetectable HCV RNA until week 12 experienced viral relapse with 48 weeks of treatment. "The results of this exploratory study suggest that a response-guided therapy may be very useful to optimize HCV treatment in patients coinfecting with HIV," the researchers concluded. "More than 48 weeks of therapy may be necessary to reduce the high risk of relapse observed among slow responders with residual viremia at week 12 of treatment."

