

AASLD 2004 Part 1



Alan Franciscus, Editor-in-Chief

This year's AASLD conference was notable for information on a wide variety of topics. Of particular interest was information on experimental therapies for hepatitis C, quality of life, and various treatment related issues.

EXPERIMENTAL HCV DRUGS

Viramidine

At this year's AASLD conference there were a couple of abstracts presented on experimental therapies that looked promising. The new drug that is farthest along in clinical trials (and the one that will most likely receive marketing approval first) is viramidine, a liver-targeting prodrug of ribavirin. Ribavirin when combined with pegylated interferon produces sustained virological results of approximately 50% for people infected with HCV genotype 1. Unfortunately, ribavirin is associated with dose-related hemolytic anemia, so research is underway to discover a drug that could produce the same type of results seen with ribavirin, but without the toxicities to red blood cells that is associated with ribavirin. Since viramidine targets the liver (prodrug), it is hoped that the concentration of it in plasma and red blood cells would

be less, but also have the same effectiveness of ribavirin in treating HCV.

One clinical trial conducted by Chin-chung Lin and colleagues compared the hemoglobin level of ribavirin and viramidine. The trial was an open-label, randomized parallel group study of 87 patients, of which 42 patients received 600 mg viramidine orally twice daily. Forty-five patients received 600 mg ribavirin twice daily if their body weights were greater than 75 kg, and 600 mg ribavirin in the morning and 400 mg in the evening if their body weights were less than 75 kg. Pretreatment, week 4 and week 12 plasma and red blood cell samples were taken.

The authors found that there was a good correlation between red blood cell and plasma concentrations of viramidine and ribavirin, but that viramidine resulted in a lower mean decrease in hemoglobin (indicating less potential for anemia) than ribavirin.

In another study, Robert Gish and colleagues reported on the end-of-treatment response rate and incidence of anemia of viramidine in combination with pegylated interferon alfa-2a (Pegasys). In the study, 180 HCV treatment naïve patients received pegylated interferon alfa-2a 180ug/



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wk in combination with viramidine at doses of 400 mg/twice daily (47 patients), 600 mg/twice daily (43 patients), 800 mg/twice daily (45 patients), or ribavirin at 1000/1200 mg daily (45 patients). The patients were predominantly male (64%) and genotype 1 (72%), mean age = 49 years old and high viral load.

The end of treatment response rates reported were comparable between all the treatment arms. Of note, the incidence of defined anemia was 2% in the viramidine 400 mg and 600mg group, 11% in the viramidine 800 mg group, and 27% in the ribavirin arm.

The authors concluded that the best safety profile and comparable efficacy was the 600 mg/twice daily in combination with pegylated interferon.

Albuferon

Albuferon is a modified interferon fused with albumin to produce a longer acting interferon. A phase I/II multi-center, open-label, dose-escalation safety trial designed to evaluate the safety, tolerability, and pharmacokinetics of Albuferon in adults infected with HCV who did not achieve

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a sustained virological response to prior HCV therapy was reported at the conference.

One hundred and nineteen patients received Albuferon in one or two subcutaneous injections, 14 days apart. It was found that the drug was well tolerated with no discontinuations due to side effects. All the side effects were transient and mild to moderate in severity.

The authors found that the viral load decline was dose-dependent and concluded that Albuferon has the potential to address the unmet need for HCV therapy with less frequent dosing than currently available pegylated interferons, and that it may offer improved clinical outcomes.

NM283

NM 283 is a polymerase inhibitor that has been found to have antiviral activity in HCV-infected chimps. A dose escalating trial was conducted in HCV patients infected with genotype 1 to evaluate the anti-HCV activity, pharmacokinetics and safety of NM283 in doses ranging from 50-800 mg/day and a placebo arm. Time period was 15 days.

Ninety-five patients in 8 cohorts were enrolled of whom 94 completed the study. HCV RNA (viral load) decline was highest in the two groups with 800 mg/day NM283 dose.

Dr. Nexam Afdhal and colleagues reported no serious adverse events, no treatment-limiting toxicities, and no pattern of laboratory abnormalities. The side effects reported were generally mild with no discontinuations. Furthermore, the authors found that NM283 is well absorbed, with dose-proportional increases in plasma concentrations. Clinical trials with NM283 alone, and in combination with pegylated interferon are

currently underway.

Dr. Afdhal also reported on the 28-day data for 19 patients enrolled in an ongoing phase IIa clinical trial of NM283 monotherapy or NM 283 plus pegylated interferon. In the patients receiving the combination therapy (12 patients) there was a 99.8 percent drop in viral load within the 28 day treatment period. The authors concluded that "(t)o date, NM 283 has demonstrated a satisfactory safety profile with no treatment-related discontinuation in either clinical trial." Originally, the trial design was for a 28 day treatment period, but it has been modified and extended to 3 months. Data from the extended protocol are expected in 2005.

Idenix is also beginning a phase IIb study of NM 283 at the end of 2004 to compare the combination of NM 283 and pegylated interferon for patients who do not respond to at least 3 months of treatment with pegylated interferon and ribavirin.

Adverse Events - Persistent Hearing Loss

It is a well known fact that pegylated interferon plus ribavirin therapy can produce moderate to severe side effects. The FDA's Center for Drug Evaluation and Research reported on a review of the FDA's Adverse Event Report System (AERS) on persistent hearing loss in patients treated with standard and pegylated forms of interferon. The estimated prevalence of the annual incidence of sudden sensory hearing loss ranges from 5-20 cases per 100,000 persons treated with interferon or pegylated interferon. However, authors pointed out that the true number of people with hearing loss from treatment may be higher because the reporting is voluntary and often the information on the adverse event report is incomplete.

The FDA undertook this study to determine if persistent hearing loss

was a potentially important pattern in interferon, and interferon plus ribavirin therapy. In this retrospective study, it was found that there were 110 unduplicated cases of hearing loss in patients receiving interferon or pegylated interferon plus ribavirin therapy. Of the 110 cases, 29 reported some degree of permanent hearing loss following treatment. The authors concluded that hearing loss, which may be persistent, will now be described consistently in all product labeling and that controlled studies are needed to find the direct relationship of interferon to hearing loss using quantifiable endpoints. It was also recommended that patients on interferon-based therapies should be monitored during treatment for changes in hearing perception. It is important to remember that the number of reported incidences was low compared to the number of patients who have received interferon-based therapies.

Any hearing loss and any other adverse event should always be reported to the FDA by the treating healthcare provider and patient. Adverse events can be reported on the FDA Web site at <https://www.accessdata.fda.gov/scripts/medwatch/> or by calling 1-888-463-6332.

Non-Invasive Liver Markers

The gold standard for gauging the health of the liver is the liver biopsy. However, the liver biopsy is an invasive procedure that has the potential for complications and is an expensive procedure.

Recent advances in diagnosing liver-related damage with various imaging and biochemical markers has produced tests that diagnose either cirrhosis or a relatively low level of damage. However, a test using various biochemical markers or imaging techniques has yet to be developed

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HealthWise:

Holidays, Alcohol, and HCV



Lucinda K. Porter, RN, CCRC

One of the first recommendations given to patients with hepatitis C virus (HCV) infection is to abstain from alcohol use. This recommendation is especially important for HCV patients undergoing antiviral therapy. Patients who drink during HCV treatment are less likely to clear the virus. The 2002 National Institutes of Health (NIH) consensus statement regarding the management of HCV advises the following:

“Alcohol is an important cofactor in the progression of HCV liver disease to cirrhosis and hepatocellular carcinoma (HCC). A history of alcohol abuse is not a contraindication to therapy; however, continued alcohol use during therapy adversely affects response to treatment, and alcohol abstinence is strongly recommended before and during antiviral therapy...safe levels of alcohol consumption are still unclear, and even moderate levels of consumption may accelerate disease progression in some patients.”

Practice guidelines established by the American Association for the Study of Liver Diseases (AASLD) concur with NIH guidelines (Diagnosis, Management, and Treatment of Hepatitis C; Doris B. Strader, Teresa Wright, David L. Thomas, and Leonard B. Seeff; HEPATOLOGY, April 2004).

“An important adjunct to the therapy of HCV is to advise chronically affected persons of measures that might be helpful in reducing or even preventing further fibrosis progression, independent of treatment. Most important is the issue of the potential deleterious effect of alcohol. There are numerous studies that have reported a strong association between the use of excess alcohol and the development or progression of liver fibrosis and even the development of HCC. Moreover, excess alcohol intake may increase HCV RNA replication and interfere with response to treatment.

Controversy exists, however, about the level of alcohol intake that is clearly harmful to the HCV infected person. It is widely believed that the daily consumption of more than 50 grams of alcohol has a high likelihood of worsening the fibrosis, but there are reports of levels of alcohol intake of less than that amount having a deleterious effect on the liver disease. Clearly, for heavy alcohol users, efforts should be undertaken to treat the alcohol abuse and dependence before starting treatment, but treatment is not contraindicated for persons who have an occasional drink of alcohol or who have a history of alcoholism. Although no consensus opinion exists, it seems reasonable to recommend either the complete suspension of alcohol intake while on treatment or to restrict the use of alcohol to an occasional drink during the course of the treatment.”

“If you are unable to quit drinking, you may need help. Alcoholism is a disease, not a character flaw.”

Alcohol abstinence is recommended for HCV patients in much the same way as it is suggested that one wear a parachute when jumping from an airplane. It is not a debatable suggestion. Yet despite this, some patients want hard facts. Can they drink a “little” or “on special occasions?” The answer to this is not known, but total

abstinence is advised. In short, why take an unnecessary risk? As one patient put it, “I view occasional moderate drinking in much the same way as Russian roulette; it’s like putting a gun to my liver, pulling the trigger, and hoping I don’t shoot myself.” One thing we know for certain, alcohol does not improve liver health.

Alcohol use is pervasive in our society. Alcohol is frequently part of social occasions, business meetings and religious ceremonies. We “toast” to health,

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luck, love, and longevity. Alcohol shows up in magazines, television, and the movies. Drinking pairs up with holidays, weddings, and sports. It is hard to imagine the Super Bowl without beer commercials.

The National Clearinghouse for Alcohol and Drug Information (NCADI) reports that nearly one-half of all persons *over the age of 11 years old* are current alcohol drinkers. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), “For most adults, moderate alcohol use—up to two drinks per day for men and one drink per day for women and older people—causes few if any problems. (One drink equals 12-ounces of beer or wine cooler, 5-ounces of wine, or 1.5 ounces of 80-proof distilled spirits.)

Certain people should not drink at all, however:

- Women who are pregnant or trying to become pregnant
- People who plan to drive or engage in other activities that require alertness and skill (such as using high-speed machinery)
- People taking certain over-the-counter or prescription medications
- People with medical conditions that can be made worse by drinking
- Recovering alcoholics
- People younger than age 21.”

Unfortunately there is a darker side to drinking. NCDAI reports that about 14 million Americans meet the criteria for a diagnosis of alcoholism or abuse. Roughly 1 in 13 adults has an alcohol problem. Alcohol abuse doesn’t just affect livers. It can threaten the immune

system, the brain, financial security, relationships, and families. In short, it can influence every aspect of life.

How do you know if you have a drinking problem? There are questionnaires that can help you identify if you have an alcohol problem (*see Resources*). NIAAA suggests using the CAGE questionnaire: “Answering the following four questions can help you find out if you or a loved one has a drinking problem:

- Have you ever felt you should Cut down on your drinking?
- Have people Annoyed you by criticizing your drinking?
- Have you ever felt bad or Guilty about your drinking?
- Have you ever taken a morning Eye-opener (drink first thing in the morning)?

One ‘yes’ answer suggests a possible alcohol problem. More than one ‘yes’ answer means it is highly likely that a problem exists. If you think that you or someone you know might have an alcohol problem, it is important to see a doctor or other health care provider right away. They can help you determine if a drinking problem exists and plan the best course of action.”

If you are unable to quit drinking, you may need help. Alcoholism is a disease, not a character flaw. There are many resources to assist those with alcohol problems, including professional, non-professional, self-help, spiritual, and secular-based approaches. If one method does not work, try another until you find one that works for you.

Whether or not drinking is a problem for you, the holidays are filled with temptations. It may be helpful to develop strategies for coping with these temptations. If

you have found it difficult to get through a social event without imbibing, devise an alcohol-free plan. Identify the triggers that cause you to drink. If talking to people is difficult, try visualizing yourself at ease in social contexts. Collect an array of conversation-starters that might be of general interest, such as the Boston Red Sox victory, the flu vaccine shortage, or whether Martha Stewart will be hosting a “decorating your cell” holiday special. Ask non-probing, open-ended questions, such as, “Do you like to travel? Have you seen any good movies lately? When I go to a party where I hardly know anyone, my goal is to encourage others to talk. I get bored listening to myself and boredom stimulates my appetite. Hearing others talk keeps my mind off of food and alcohol.

I don’t like feeling deprived, so when I go to a holiday party, bottled water is just not festive enough. My favorite “throw caution to the wind” drink is a Shirley Temple with at least 2 maraschino cherries. Here are some other non-alcoholic drinks:

- Tonic with a twist of lemon or lime
- Tomato juice with a dash of Tabasco and a slice of lemon
- Club soda or seltzer on the rocks with an olive
- Cola with lemon or lime
- Hot chocolate topped with whipped cream
- Hot apple cider with a cinnamon stick
- Carbonated water with grenadine and a wedge of lemon, lime, or orange
- A “virgin” version of any favorite mixed drink, such as a non-alcoholic piña colada
- A non-alcoholic beer with lemon (*Caution: non-alcoholic*

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HIV/HCV Coinfection: *Summary from ICAAC & AASLD*



Liz Highleyman

Several presentations at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the American Association for the Study of Liver Diseases (AASLD) meeting, both held in late October early November 2004, dealt with hepatitis C and HIV coinfection.

TREATMENT OF COINFECTED INDIVIDUALS

Following on the heels of the APRICOT and ACTG 5071 studies, the PRESCO (Pegasys Plus Ribavirin for HCV Treatment in HIV/HCV Coinfection) trial (ICAAC abstract V-1148) again showed promising results using pegylated interferon plus ribavirin to treat HIV/HCV-coinfected individuals. This ongoing multicenter study by M. Núñez and colleagues from Madrid's Hospital Carlos III includes about 350 subjects with well-controlled HIV disease and good overall health; about half have hard-to-treat HCV genotype 1, about 40% have genotypes 2 or 3, and about 10% have genotype 4. This study used relatively high weight-adjusted doses of ribavirin (low initial doses of ribavirin may have contributed to the high relapse rate seen in ACTG 5071). The present analysis included nearly 200 patients who completed 24 weeks of therapy. After 24 weeks, an intent-to-treat analysis revealed that 63% of all subjects and 50% of those with genotype 1 achieved undetectable HCV viral

loads. As-treated response rates were higher (71% overall and 61% for genotype 1), since this analysis excluded the approximately 20% of subjects who discontinued therapy early due to adverse events or other causes. While this response rate for genotype 1 patients is higher than those seen with the same duration of treatment in other coinfection studies, longer follow-up is needed to determine whether participants will go on to achieve sustained virological response (SVR) 24 weeks after the completion of therapy.

WHEN TO STOP HCV TREATMENT

Given the difficult side effects and high cost of hepatitis C treatment, it would be useful to predict which patients are likely to achieve SVR so therapy can be stopped early in people who will not benefit. Two presentations at ICAAC showed that as is the case with HCV-monoinfected individuals coinfecting patients who respond poorly early in the course of therapy usually do not go on to achieve SVR. Maribel Rodríguez-Torres and colleagues (ICAAC abstract H-1751) analyzed data from a subset of nearly 300 subjects in the APRICOT study (about 60% with genotype 1). They found that while a good response (at least a 2-log drop in HCV RNA) at week 4 or week 12 did not necessarily predict SVR (positive predictive value of 66% and 56%, respectively), a poor response at these time points

did predict lack of SVR (negative predictive value of 88% at week 4 and 98% at week 12). The researchers concluded that 12 weeks was the best time to assess progress and make a decision about continuing therapy, since four weeks seemed to be too early and missed some people who would later achieve SVR. Early response data from the PRESCO study (ICAAC abstract H-1753) support a similar conclusion. Manel Crespo presented similar findings at AASLD (abstract 428), again validating a 2-log HCV RNA decrease at week 12 as a useful predictor of ultimate treatment success. In contrast, however, a small study by E. Shaw and colleagues (ICAAC abstract H-1752) found that no patients who failed to demonstrate at least a 1-log drop in HCV RNA by week 4 later achieved SVR (negative predictive value of 100%).

LOW-DOSE INTERFERON

Another way to limit side effects related to hepatitis C treatment is to use lower doses of interferon and/or ribavirin, but there is concern that this strategy may compromise the effectiveness of therapy. Ghasan Hammoud reported at AASLD (abstract 520) that in a study of 63 coinfecting individuals (about half black, about one-quarter with genotype 1), subjects who received low-dose (1.0 mcg/kg/week) pe-

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that accurately measures all levels of liver damage. On firmer ground are tests that measure cirrhosis. A new test called FibroScan® was reported on at AASLD and the results look promising.

E. Chanteloup and colleagues presented a poster on FibroScan®, a new non-invasive method for the detection of cirrhosis and complications in patients with chronic liver diseases. This on-going prospective study compared patient liver stiffness to clinical, biological, morphological and histological parameters using Spearman coefficient or correlation. The poster reported on 456 patients (257 males, mean age 53 ± 13 years) included to date in the study. The patient population of this study included patients with chronic liver disease was: hepatitis C ($n = 27$), hepatitis B ($n = 21$), alcohol ($n = 66$), non-alcoholic steatohepatitis ($n = 66$). The authors found that liver stiffness was significantly correlated to fibrosis stage, clinical patterns (previous bleeding varices, ascites, hepatocellular carcinoma, Child-Pugh score), biological parameters (platelets, prothrombin time, V factor, albumin, and bilirubin) and morphological parameters (oesophageal varices, splenomegaly) and dysmorphism. The authors concluded that FibroScan® is a promising new non-invasive method for the detection of cirrhosis and its complications in patients with chronic liver disease.

Exercise

Exercise is an important tool for managing HCV-related fatigue both on and off of HCV medical treatment. A study by Donna M. Zucker, RN, PhD, reported on a small trial of 20 HCV positive patients about to start combination therapy, designed to

examine the relationship between an exercise intervention, and completion of combination therapy (for 24 or 48 weeks), fatigue, quality of life (QOL), and walking distance in patients with chronic hepatitis C. The patients were randomly assigned to the exercise group or to a control group that received the usual care. The exercise group began self-paced home walking for 3 weeks prior to starting HCV therapy (interferon plus ribavirin). Self-reported fatigue, quality of life, a 12 minute walk, and completion of treatment were measured in both groups. As well, phone and office support was offered bimonthly to both groups.

The author found that exercise intervention was effective, although the initial dose set for each participant varied. A small to moderate effect size was calculated for the walking intervention relative to the completion of HCV combination therapy, reduction of fatigue, increased quality of life, and walking distance. Importantly, self-reported fatigue was less in the exercise group than in the control group. In addition, the Hepatitis Quality of Life Questionnaire subscales for hepatitis specific limitations and distress were increased in the exercise group and relatively unchanged in the control group. The author also noted that exercise may promote health as well as enhance rates of adherence to HCV medical therapy and that a future study will enroll patients taking pegylated interferon plus ribavirin.

Fatigue and Sleep Disturbances

It is estimated that 40-60% of people with hepatitis C self-report fatigue and sleep disturbances, which can greatly impact quality of life. Meghan Carlson and colleagues reported on a study that evaluated fatigue using the Fatigue Severity Scale (FSS) and the Pittsburgh Sleep Quality Index (PSQI) to assess subjective sleep quality.

Eighty consecutive chronic hepatitis C patients attending University of California at San Diego Adult Liver Clinics were included in the study and completed the FSS and PSQI questionnaires. The patient population was 53% males, 55% Caucasian, 34% Latino, and 3.4% African-American. Mean age and education were 51.9 ± 9.18 and 13 ± 3.31 years respectively. Forty-one patients were non-cirrhotic and 39 were cirrhotic. No patients were receiving antiviral therapy at the time of assessment.

The authors reported that the FFS scores indicated greater fatigue than past reports of normal health adults and patients with chronic hepatitis C. It was also found that there were no significant differences between cirrhotic and non-cirrhotic patients on the FSS and PSQI global score. It was found that there was a correlation between the FSS score (fatigue) and the global PSQI (sleep disturbances) score. Interestingly, non-cirrhotic patients showed a greater use of sleeping medications when compared to cirrhotic patients.

The authors concluded that sleep disturbances and fatigue were common in all patients with hepatitis C in this study.

Cryoglobulinemia

Cryoglobulinemia is one of the most common extrahepatic manifestations of hepatitis C. Although many people with hepatitis C test positive for cryoglobulinemia, most are asymptomatic. But for people with symptomatic cryoglobulinemia, this autoimmune disease can have serious consequences that could lead to kidney damage and recently it has been linked to Non-Hodgkins lymphoma. Symptoms can include muscle and joint pain, skin rash, fever, kidney damage, and ulcerations of the fingers and toes. Cryoglobulinemia

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is caused by the body's production of anti-bodies to the hepatitis C virus.

A recent study at the conference reported on the central nervous system's involvement in patients with HCV related cryoglobulinemia. The study included 40 HCV positive patients with cryoglobulinemia compared with 11 hepatitis C positive controls and 36 healthy volunteers, matched for sex and age. A battery of 10 standardized neuropsychological tests was administered by one experienced neuropsychiatrist. All patients underwent MRI testing.

The authors reported that 34 (94%) of the patients evaluated had a deficiency in one or more of the 10 cognitive domains examined. The most commonly involved domains were those of attention (68%), executive functions (41%), and visual construction and visual spatial functions (35%). The incidence of impaired cognitive function was significantly higher in the cryoglobulinemia than the HCV control group. The MRI analysis showed that the group with cryoglobulinemia had a higher mean number of total and peri-ventricular white matter high intensity signals than HCV controls and healthy volunteers.

The authors concluded that the high frequency of impaired cognitive function and the extent of MRI brain abnormalities in patients with HCV-associated mixed cryoglobulinemia strongly suggests a specific inflammatory involvement of the central nervous system.

Part 2 of this article on the AASLD conference will discuss interferon-based therapies.

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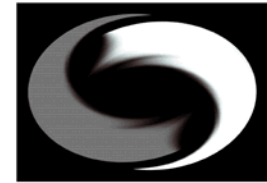
beers and wines are usually prohibited for those in addiction recovery or organ transplant programs)

- Drink from nice glassware. Sparkling water from a wine glass adds a touch of elegance.

May your holiday season be festive, healthy, and alcohol-free followed by a happy New Year.

Resources

- *Alcoholic Anonymous (AA)*
www.alcoholics-anonymous.org
To find an AA group near you, look for "Alcoholics Anonymous" in any telephone directory or contact AA World Service, PO Box 459, New York, NY 10163; (212) 870-3400
- *American Council on Alcoholism*
www.aca-usa.org
Nationwide HelpLine 800.527.5344
- *National Institute on Alcohol Abuse and Alcoholism (NIAAA)*
www.niaaa.nih.gov
5635 Fishers Lane, MSC 9304
Bethesda, Maryland 20892-9304
- *National Clearinghouse for Alcohol and Drug Information (NCADI)*
www.health.org
(800) 729-6686
- *National Drug Treatment and Referral Routing Service*
(800) 662-HELP (4357)
- *Substance Abuse and Mental Health Services Administration (SAMHSA)*
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glylated interferon (Peg-Intron) plus weight-adjusted ribavirin for 48 weeks responded about as well as those who received a higher Peg-Intron dose (1.5 mcg/kg/week). However, these results must be interpreted with caution since both end-of-treatment response and SVR rates were unusually low (27% and 11%, respectively) in this study compared to those seen in other recent coinfection trials.

HISTOLOGICAL RESPONSE

Looking at histological response in the APRICOT trial, Eduardo Lissen and colleagues (AASLD abstract 174) found that while SVR (40% overall) correlated with improved liver fibrosis, a “substantial proportion” of patients experienced histological improvement even in the absence of SVR. Improvement in liver health was seen in 69% of those who achieved SVR and in 43% of those who did not achieve a sustained response.

SIDE EFFECTS OF HCV THERAPY

L. Moreno and colleagues (ICAAC abstract V-0784) reported that many coinfecting individuals with advanced fibrosis experience severe side effects when using interferon plus ribavirin, but some can still benefit from hepatitis C treatment. In this prospective study of 56 subjects, 88% were on combination anti-HIV therapy and most had well-controlled HIV disease (although 18% had an AIDS diagnosis); 59% had genotype 1 HCV, and 43% had evidence of cirrhosis. At the end of HCV treatment (just over three-quarters with pegylated

interferon), 29% experienced an end-of-treatment response, but only 14% achieved SVR. More than one-quarter (29%) discontinued treatment due to side effects; one-fifth of the subjects were hospitalized and two (4%) died during therapy. Blood cell deficiencies were particularly common: neutropenia, 73%; thrombocytopenia, 61%; anemia, 38%. The poor results seen in this study may be related to the fact that a substantial number of the subjects had a history of injection drug use and returned to active use during HCV treatment. Because some individuals responded well to treatment, however, the researchers suggested interferon plus ribavirin

“Improvement in liver health was seen in 69% of those who achieved SVR and 43% of those who did not achieve a sustained response.”

could be a viable option for patients with advanced liver disease.

In other side effects reports, Ana Rendón, also from the Hospital Carlos III team, reported that levels of ribavirin in the blood could predict which patients would develop anemia during treatment (ICAAC abstract H-1754). Although all 49 people in this analysis received the same weight-adjusted doses of ribavirin (1000 mg if under 75 kg, 1200 if above this weight), blood levels of the drug varied widely among individuals. Not surprisingly, patients with higher ribavirin blood concentrations were more likely to develop anemia. These results suggest that drug level monitoring could play a role in managing HCV treatment

side effects. In related research, Lev Ginzburg (AASLD abstract 397) reported that women and people over age 55 were at higher risk of anemia while taking ribavirin than men and younger individuals.

LIVER TOXICITY DUE TO HIV THERAPY

In terms of liver toxicity related to HIV therapy, C. Cooper and colleagues (ICAAC abstract H-1759) found that, based on a chart review of HCV positive patients at Ottawa Hospital treated with anti-HIV drugs between January 1994 and December 2003, severe liver toxicity was uncommon. Just 7% developed an ALT level more than five times the upper limit of normal, and only 3% switched or discontinued HIV medications due to liver problems (all of these were taking full-dose protease inhibitors, not non-nucleoside reverse transcriptase inhibitors or low “boosting” doses of ritonavir [Norvir]). L. Aranzabal from Ramón y Cajal Hospital in Madrid (ICAAC abstract H-1760) reported,

based on a study of 107 coinfecting patients, that individuals with moderate-to-advanced liver damage (Knodel fibrosis scores of 3 or 4) were nearly three times more likely to experience severely elevated ALT than patients with less fibrosis. In related research, J. Sasadeusz (AASLD abstract 372) reported that Pegasys plus ribavirin “appears to be safe and well-tolerated” in coinfecting subjects in the APRICOT trial who had compensated cirrhosis. However, two subjects with decompensated cirrhosis died during the study, leading the researchers to urge caution in such patients.

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LIVER TRANSPLANTATION

Several studies to date have shown that people with HIV have liver transplant outcomes nearly or as good as those of HIV-negative people. But new research indicates that current algorithms for allocating donor organs may work to the disadvantage of HIV positive and coinfecting individuals. A study by M. Sánchez-Conde from the Hospital Carlos III team (ICAAC abstract H-1758) found a disproportionately high mortality rate among coinfecting HIV patients on liver transplant waiting lists (4 out of 20, or 20%), and suggested that HIV positive individuals with cirrhosis should be assessed and added to waiting lists

“much earlier” than their HIV-negative counterparts. In related news, Isabelle Pache (AASLD abstract 442) reported that more than half (58%) of HIV/HCV-coinfecting patients with cirrhosis met the criteria for transplantation, but that 29% died either before evaluation or while waiting for a new liver. Pache and colleagues suggested that since liver damage progresses more rapidly in coinfecting individuals, a “more specific and sensitive criteria” than the MELD score should be defined for coinfecting patients, and that such individuals “should be referred early in the course of the liver disease to a liver transplantation unit.”



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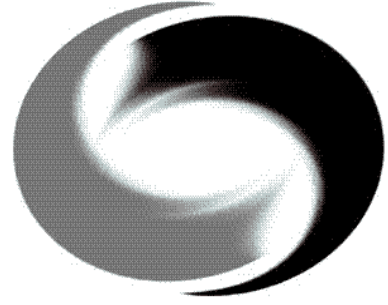
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