New HCV Therapies May Aid Nonresponders

Interferon is likely to remain the basis of treatment, even if the new antiviral agents prove useful.

BY TIMOTHY F. KIRN
Sacramento Bureau

CHICAGO — Watchful waiting may be the prudent approach now when a patient with hepatitis C does not respond to standard interferon treatment, speakers said at the annual Digestive Disease Week.

That's because a number of promising new approaches and treatments are on the horizon, including longer treatment regimens, a ribavirin prodrug called viramidine, hepatitis C virus protease and polymerase inhibitors, antifibrotic agents, and new interferons.

Currently, about 45% of patients treated with the standard regimen of weekly pegylated interferon-alfa-2a with daily ribavirin given for 48 weeks will not respond adequately, said John B. Gross Jr., M.D., of the Mayo Clinic, Rochester, Minn.

Factors known to be associated with treatment failure include infection with hepatitis C virus genotype 1, a high viral load, advanced hepatic fibrosis or cirrhosis, obesity, underdosing to counter side effects or nonadherence to treatment, and African American race.

With regard to underdosing and lack of adherence, it has been shown that a pronounced response to treatment within the first 12 weeks indicates a high likelihood of a sustained virologic response. When a patient is at least 80% tolerant to initial dosing and adherent to treatment during those first 12 weeks, the percentage of patients achieving a sustained response goes up from about 40% overall to 60%. But when the dose of both drugs needs to be lowered, the percentage drops to 33%, Dr. Gross noted.

Some researchers have been looking at weight-based dosing of ribavirin, which appears to improve the virologic response rate. Others are studying treatment beyond the usual 48 weeks, which appears to cut the relapse rate. The results of those studies are still preliminary, he noted.

Some patients who have not responded to initial interferon therapy probably can be treated again. Patients who would be candidates for a second round of treatment are those who were treated before the pegylated interferon era or combined interferon-ribavirin treatment, or those who were nonadherent the first time.

"It turns out the predictors of a more sustained viral response in this group are just the same as for treatment-naive patients," Dr. Gross said.

Patients with advanced cirrhosis probably should be enrolled in a clinical trial, he added. But most patients probably should just wait for future developments, with a liver biopsy scheduled for some future date.

Gary L. Davis, M.D., said interferon is likely to remain the basis of treatment even if the new antiviral agents now are in development prove useful.

Interferon will be necessary to combat the drug resistance that will undoubtedly arise with any new antiviral drug, said Dr. Davis of Baylor University, Houston.

At the meeting, early studies were presented on two new types of interferon, pegylated consensus interferon, which is a bioengineered interferon that can be given at a high dose, and an albumin-interferon fusion protein, which has a long half-life and would be given only once every 2-4 weeks. Both had good results in phase I or phase II trials, he said.

The antiviral drugs under study include viramidine, a precursor drug to ribavirin thought to cause less anemia, and several protease and polymerase inhibitors.

In a phase II trial presented at the meeting, viramidine did show a reduced incidence of anemia, Dr. Davis noted. In that trial, 27% of ribavirin-treated controls developed anemia. In comparison, no patients who received the lowest dose of viramidine (400 mg daily) developed anemia and only 2% of those who received the middle dose (600 mg) developed anemia. Of those who received the highest dose, 11% developed anemia, a difference that was not statistically significant.

The 171-patient study was perhaps not large enough to address efficacy with certainty, and many patients dropped out. But the results suggest that the proportion of patients who achieved a virologic response at the end of treatment was similar in all of the groups, and there was less relapse 24 weeks after treatment in those treated with viramidine, reported Robert G. Gish, M.D., of the California Pacific Medical Center, San Francisco.

Some of the protease and polymerase inhibitors being investigated appear powerful, but they are just now entering meaningful clinical trials, Dr. Davis said.

The agents shown in the laboratory to have antifibrosis capability include some that are already available, such as pentoxifylline, sirolimus, and vitamin E, Dr. Davis and Dr. Gross said. But it will be difficult to evaluate them in the clinic because of the lack of good markers of fibrosis. ■

Hepatocellular Carcinoma Treatment Underused in U.S.

BY TIMOTHY F. KIRN
Sacramento Bureau

CHICAGO — Only 13% of U.S. patients diagnosed with hepatocellular carcinoma receive potentially curative therapy, Hashem B. El-Serag, M.D., said at the annual Digestive Disease Week.

Moreover, only one-third of those with single lesions get potentially curative therapy, said Dr. El-Serag of Baylor College of Medicine, Houston.

In other countries, potentially curative therapy appears to be used at much higher rates. Such treatment was provided for 40% of all hepatocellular carcinoma patients in a series from Barcelona and 30% of all patients aged over 75 years in Italy.

"There is significant underutilization of potentially curative therapy, even among those with favorable clinical features," said Dr. El-Serag, who, with his colleagues, examined data for a nationwide cancer registry that is now linked to Medicare data. "The reasons for this observation need to be examined and corrected."

Dr. El-Serag's study included data from 2,963 patients with hepatocellular carcinoma diagnosed between 1992 and 1999. The patients were entered into any 1 of 11 different regional cancer registries.

In addition to the 13% of patients who received potentially curative therapy, 4% received transarterial chemoablation and 35% received systemic chemotherapy or radiotherapy. The other 48% of the patients received no treatment at all.

The study found that age and ethnicity affected which patients received potentially curative therapy. Among those aged 65-74 years, the rate of the use of potentially curative therapy was 17%, and among racial groups, Asian people had the highest rate of potentially curative therapy—24%—apparently because they had more single and small tumors.

But neither of those characteristics had as strong an influence on rate as did the region where the cancer was diagnosed, Dr. El-Serag said, although he did not identify which regions had the highest or lowest rates.

The rates of attempted therapy did increase over time in the study, but this improvement was not dramatic, he added. For example, between 1992 and 1995, 53% of patients received no treatment. But the rate fell to 43% between 1996 and 1999.

Many physicians have too dismal a view of the prognosis of hepatocellular carcinoma, and that perception does not appear to have changed much between 1999 and the present, Dr. El-Serag said. Specifically, the majority of physicians still do not know that liver transplantation is an option for liver cancer, he added. ■

Cholecystectomy Improved Outcomes, Was Safe in Older Gallstone Patients

BY KATHLEEN LOUDEN
Contributing Writer

CHICAGO — Cholecystectomy should be performed after endoscopic removal of bile duct stones in patients older than 60 years who also have gallstones, James Lau, M.D., said at the annual Digestive Disease Week.

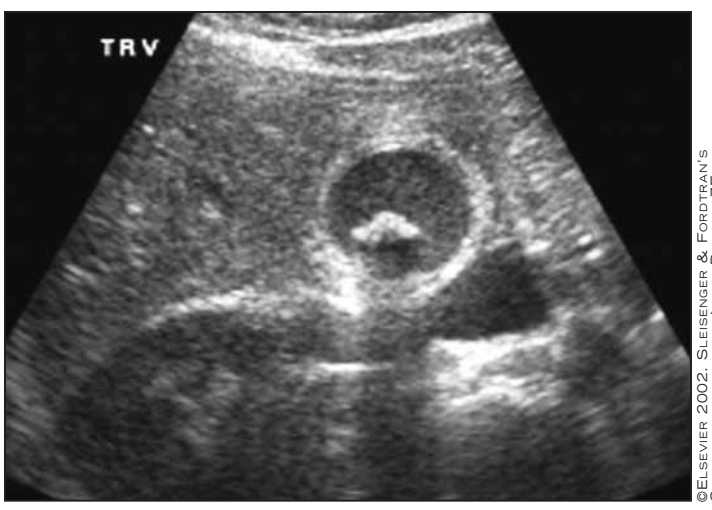
Surgical removal of the gallbladder, performed either traditionally or endoscopically, significantly reduces recurrent biliary events, compared with those that occur when the gallbladder is left in situ, Dr. Lau reported.

"There is a perceived high morbidity with cholecystectomy in patients older than 60," said Dr. Lau of Prince of Wales Hospital and Chinese University of Hong Kong. However, he and his associates found that this was not the case.

The researchers randomly assigned 178 patients older than 60 who had concomitant gallstones (pigment stones) to either cholecystectomy or expectant management following endoscopic sphincterotomy and clearance of bile duct stones. Of those, 82 patients elected to have cholecystectomy, and 88 patients kept their gallbladder and were managed with watchful waiting.

During a median follow-up of 66 months, six patients (7.3%) in the cholecystectomy group returned for treatment of biliary events, primarily cholangitis, Dr. Lau reported. In the observation group, 21 patients (24%) experienced recurrent events, including bile duct stones and cholangitis, acute cholecystitis, or biliary colic. Additionally, more persons in the observation group died than did those who underwent cholecystectomy (19 vs. 11), he said.

In recommending cholecystectomy in this older patient population, Dr. Lau cautioned that the conversion rate from laparoscopic to open cholecystectomy is expected to be high. Conversion to open surgery was needed in 16 (20%) of the 82 patients. ■



Cholecystectomy benefited patients who had bile duct stones removed and also had gallstones, shown here by sonography.

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