Treatments Coming for Resistant Hepatitis C

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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.

Regarding 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 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 from about 40% 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 virologic response. Others have been 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 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 showed 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. ■