

Triple therapy has poor safety in cirrhotic hepatitis C

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BOSTON – In patients with chronic hepatitis C virus infections and compensated cirrhosis, a combination of a direct-acting antiviral agent, pegylated interferon, and ribavirin produced high on-treatment virologic response rates, but at the cost of significantly increased toxicities in an interim analysis of a French multicenter trial looking at the safety of the regimen.

Although the efficacy of direct-acting antiviral regimens involving the protease inhibitors telaprevir (Incivek) and boceprevir (Victrelis) combined with pegylated interferon alfa-2a or -2b in combination with ribavirin (PEG-IFN/RBV) in cirrhotic nonresponders to prior therapy was good, their safety was "poor," according to Dr. Christophe Hézode of the Hôpital Henri Mondor in Créteil, France.

Virologic response at 16 weeks in a per-protocol analysis was associated with a virologic response rate of 92% with telaprevir and 77% with boceprevir.

However, there were increased rates of serious adverse events and more difficult-to-manage anemia than in phase III trials for telaprevir and boceprevir, which included only a few patients with cirrhosis, Dr. Hézode said at the annual meeting of the American Association for the Study of Liver Diseases.

In treatment-experienced cirrhotic patients with platelet counts of 100,000/mm³ or serum albumin levels below 35 g/L, clinicians should weigh the risks and benefits of such regimens, with patients treated on a case-by-case basis because of the high risk for severe complications, Dr. Hézode said.

"However, cirrhotic experienced patients without predictors of severe complications clearly should be treated, but cautiously and carefully monitored," he added.

Dr. Hézode and his coinvestigators in the French Cohort of Therapeutic Failure and Resistances in Patients Treated With a Protease Inhibitor (telaprevir or boceprevir), Pegylated Interferon, and Ribavirin (CUPIC) trial studied two cohorts of patients with chronic hepatitis C virus (HCV) infections, and compensated cirrhosis (Child Pugh class A) who had either relapsed or had only a partial response to prior therapy, with partial response defined as at least a 2 log₁₀ decline in V RNA but failure to clear virus by week 24.

He presented data on 497 patients who had completed 16 weeks of therapy on one of two regimens. In one cohort, 292 patients received 12 weeks of telaprevir 750 mg every 8 hours, and PEG-IFN alfa-2a (Pegasys) 180 mcg/wk with ribavirin 1,000-1,200 mg/day, followed by PEG-IFN/RBV through 48 weeks. In the second cohort, patients received a 4-week initiation phase with PEG-IFN alfa-2b (PegIntron) and ribavirin, followed by 44 weeks of boceprevir 800 mg every 8 hours, PEG-IFN 1.5 mcg/kg per wk, and ribavirin 800-1,400 mg/day.

At week 16, 45% of patients on telaprevir had had at least one serious adverse event, with 14.7% terminating therapy because of a serious side effect. In all, nearly one-fourth (22.6%) discontinued therapy, and there were five deaths: from septicemia, septic shock, pneumopathy, endocarditis, and bleeding esophageal varices. Other complications in this group included grade 3 or 4 infections in 6.5%, grade 3 or 4 hepatic decompensation in 2%, grade 3/4 asthenia in 5.5%, and renal failure in 1.7%.

Hematologic adverse events included anemia of grade 2 or greater in 30.4%, erythropoietin use in 53.8%, blood transfusion in 16.1%, and ribavirin dose reduction in 13%. In addition, 2.7% of patients had grade 3 or 4 neutropenia, and 1.7% had grade 3 or 4 thrombocytopenia.

In the boceprevir group, 32.7% had at least one serious adverse event, 26.3% discontinued prematurely, and 7.3% discontinued because of serious events. The cause of one death was described as pneumopathy. Grade 3/4 adverse events involved infections in 2.4%, hepatic decompensation in 2.9%, and asthenia in 5.8%. There were no cases of renal failure in this group.

Hematologic events in patients on boceprevir included grade 2 or greater anemia in 27.8%, erythropoietin use in 46.3%, blood transfusion in 6.3%, and ribavirin dose reduction in 10.7%.

Grade 3/4 neutropenia was seen in 4.4%, and grade 3/4 thrombocytopenia in 5.4%. Two patients (1%) in this cohort received thrombopoietin.

In a multivariate analysis, significant baseline predictors of severe complications (death, severe infection, and hepatic decompensation) included platelet counts of 100,000/mm³ or lower (odds ratio, 3.11; P = .0098) and a serum albumin level below 35 g/L (OR, 6.33; P less than .0001).

Baseline predictors for severe anemia (hemoglobin less than 8 g/dL) or blood transfusion included female gender (OR, 2.19; P = .023), no lead-in phase (OR, 2.25; P = .018), age 65 years or older (OR, 3.04; P = .0014), and hemoglobin 12 g/dL or lower for women and 13 g/dL or lower for men (OR, 5.30; P less than .0001),

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