Erythropoietin for HCV May Lack Clinical Benefit

The drug's expense along with its unproven survival benefit are enough to signal caution in many settings.

BY MICHELE G. SULLIVAN
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BOSTON — Erythropoietin is quickly becoming an integral part of hepatitis C treatment regimens, despite a lack of firm data supporting its long-term clinical benefit, Dr. Eric Yoshida said at the annual meeting of the American Association for the Study of Liver Diseases.

Only a few studies have prospectively examined the effect of erythropoietin in these patients, and whereas the studies have shown statistically significant improvements in terms of increasing hemoglobin levels and allowing for maintenance of ribavirin dosage, opinions vary on whether these differences translate into clinical benefit.

"Does this mean there is no place for erythropoietin for these patients? No, I don't think so. I think what it means is that we should treat the patient—not the numbers," said Dr. Yoshida, head of gastroenterology at the University of British Columbia, Vancouver.

Ribavirin, considered a mainstay of antiviral therapy for hepatitis patients, can cause a dose-dependent hemolytic anemia.

Guidelines suggest decreasing the dosage of ribavirin when hemoglobin levels fall below 12 g/dL, and discontinuing the drug if levels fall below 8.5 g/dL.

But because ribavirin is so important to sustained viral response, some patients persist with their ribavirin even when they develop an anemia that significantly impairs their quality of life, Dr. Yoshida said.

He reviewed three studies that have examined the effect of erythropoietin in hepatitis C patients.

The first study, a 2003 placebo-controlled trial, randomized 64 patients to either standard of care (placebo) or weekly erythropoietin injections for 16 weeks. At baseline, the mean hemoglobin level was 11 g/dL in both groups (Am. J. Gastroenterol. 2003;98:2491-9).

At the study's end, patients receiving erythropoietin had significantly higher mean hemoglobin levels (14 g/dL versus 11 g/dL). Additionally, ribavirin dosage was similar in both groups, indicating that those taking the study drug were able to maintain their ribavirin dosage.

By the end of the trial, undetectable HCV RNA was seen in 69% of erythropoietin-treated patients and 60% of placebo patients. However, Dr. Yoshida pointed out, there was an unexpectedly high dropout rate (42% of erythropoietin patients and 50% of placebo patients). The dropout rate makes it difficult to conclude that the difference in percentage of patients with undetectable HCV RNA was related to erythropoietin therapy.

A second study, published in 2004, randomized 185 patients to placebo or erythropoietin for 8 weeks. After 8 weeks, eligible patients from both groups entered into an 8-week open-label trial (Gastroenterology 2004;126:1302-11).

By the end of the first 8 weeks, significantly more erythropoietin-treated patients than placebo patients were still taking their baseline ribavirin dose (88% versus 60%, respectively). At the end of the crossover phase, prior placebo patients had increased their ribavirin dosage significantly, from a mean of 852 mg/day to a mean of 921 mg/day.

Baseline hemoglobin levels (11 g/dL in both groups) rose to 13 g/dL in the erythropoietin group by the end of the first 8 weeks, but remained unchanged in the placebo group.

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By the end of the open-label phase, mean hemoglobin levels in prior placebo patients were the same as those in patients who had taken erythropoietin for the entire study (13 g/dL).

A post hoc analysis concluded that erythropoietin-treated patients also reported significant improvements in their quality of life (Hepatology 2004;40:1450-8). The importance of quality-of-life benefits should not be underestimated in hepatitis patients, Dr. Yoshida said, because quality-of-life scores of HCV patients on treatment can be lower than those of patients with diabetes and heart failure.

The study did not find significant differences between groups in HCV RNA levels.

These trials raise yet more questions, Dr. Yoshida said. The hemoglobin level that should trigger erythropoietin treatment is still unclear. "Should the availability of erythropoietin change the hemoglobin threshold, especially when improved undetectable HCV RNA, sustained viral response, and survival have not been documented with its use?" Others might argue that starting the drug when patients have higher hemoglobin levels that are just starting to slide would be beneficial, he said.

There are also no firm data on the duration of erythropoietin treatment that is beneficial, and the studies performed to date offer little guidance.

The drug is expensive as well, adding almost $16,500 per year to the cost of treatment for hepatitis C, according to a cost-effectiveness study that Dr. Yoshida cited (Clin. Gastroenterol. Hepatol. 2005;3:1034-42). But that study also concluded that if a third-party payer covered $50,000 for every quality-of-life year gained with erythropoietin therapy, 86% of patients would still be treated "within budget."

Still, noted Dr. Yoshida, the drug's expense along with its unproven survival benefit are enough to signal caution to many health care providers, especially those in countries with socialized health care systems.

"Hopefully, future trials will address these questions," he said.

Dr. Yoshida's review was summarized in the Annals of Pharmacotherapy (2007; 41:268-75).

He declared no financial interest in any hematopoietic agent.

Hepatitis C Infection Rate Surges in Canada and the U.S.

BY KATE JOHNSON
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MONTREAL — The escalating numbers of new and existing hepatitis C infections in Canada are reinforcing the evidence of a U.S. epidemic, Dr. Robert P. Myers said at Canadian Digestive Diseases Week.

"The burden of hepatitis C has grown dramatically in the past decade," said Dr. Myers of the University of Calgary (Alta). "It is vital that we continue with preventive measures and maximize treatment."

By using an administrative hospitalization database from the Calgary Health Region, Dr. Myers identified 4,002 hospitalizations related to hepatitis C virus (HCV) infection between 1994 and 2004, 22% of which (869 cases) were HCV liver-related, he reported. Among this group of patients, 67% were male, with a median age of 50 years.

With a concentration on number of hospitalizations, length of hospital stay, and in-hospital mortality, Dr. Myers documented an approximate fourfold increase over the 11-year period. Hospital charges for this population also increased an average of 41% between 2000 and 2004, which was attributable to more admissions rather than longer hospital stays. The length of stay actually stabilized during this period, at an average of 7 days, he said.

"We project if this rate continues in a linear fashion that by 2020, across Canada, about $240 million [Canadian] will be spent on hepatitis C liver-related hospitalizations," he said.

'The burden of hepatitis C has grown dramatically in the past decade. It is vital that we continue with preventive measures and maximize treatment.'

Patient subgroups that were identified as particularly high risk included females, who represented 25% of the hospitalizations at the beginning of the study period but increased to 35% by the end, for an average annual increase of 19%.

"Interestingly, if you compare that to the males, somewhat counterintuitively males had a lower annual growth rate in hospitalizations of 13.1%," he said. "The etiology of that is a bit unclear, but it may perhaps be due to underreporting at the beginning of the study." He noted that even when adjustments were made to account for underreporting, the findings remained significant.

Other high-risk groups were patients aged 40-59 years, for whom hospitalizations increased more than in any other age group, at 19% annually, and HIV-coinfected patients. The latter accounted for about 1% of hospitalizations at baseline, but made up 6% of hospitalizations by the end of the study, he said.

Dr. Myers noted that recent projections about the burden of HCV in the United States are very similar to his findings. According to a calculation model based on epidemiologic data from the U.S. Centers for Disease Control and Prevention, mortality related to HCV is likely to increase over the next 25 years (J. Viral Hepat. 2007;14:107-15). The study estimated that the number of cases has risen from about 3,700 in 1998, and will peak at about 13,000 in 2030. Similar Canadian projections have been reported.

A separate study reported at the meeting was based on a unique, province-wide data system to estimate the rate of new cases of HCV infection in British Columbia. The British Columbia Centre for Disease Control laboratory data from 1992-2005 enable the researchers to document positive HCV results in people who previously tested negative, said Margot Kuo, Ph.D., from the University of British Columbia, Vancouver. As such, it offers a unique picture of testing practices and seroconversion trends.

Her analysis identified a significantly higher incidence of newly acquired infection than had been previously reported, with the highest incidence in 20- to 29-year-olds and 30- to 39-year-olds at 13.6 and 11.3 cases per 100,000, respectively.

"The effect of gender on the rates was not consistent across all ages," she noted. "Males had a slightly higher incidence across all age groups except teens. We were picking up HCV seroconversion among teen females four times more frequently than among teen males." This was reflected in an incidence of 5 cases per 100,000 in teen females, compared with 1.3 cases per 100,000 in teen males.

"While this could mean that teen females are at higher risk, it's likely related to testing patterns," she commented. "Teen males have a very low rate of testing and display very low repeat test behavior, while females tend to test more, and have more repeat tests." Nevertheless, the finding has important implications for the development of prevention strategies, she said.