Growth Factors Bolster Hepatitis Tx Compliance

BY DENISE NAPOLI

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Having cirrhosis, diabetes, or substance use disorder increased the odds of treatment discontinuation in type 1 hepatitis C virus infection, but use of growth factor drugs correlated with treatment persistence, reported Dr. Lauren A. Beste and colleagues.

The investigators looked at 11,019 patients in the VA health care system with hepatitis C genotype 1 who received at least two prescriptions for pegylated interferon and ribavirin between Jan. 1, 2002, and Dec. 31, 2007.

Patients who completed at least 80% (38.4 weeks) of the standard 48-week treatment regimen were considered to have completed treatment; overall, 5,795 patients (52.6%) reached this goal (Clin. Gastroenterol. Hepatol. 2010 November [doi:10.1016/j.cgh.2010.07.012]).

Although "no indications currently exist for discontinuing treatment [before 12 weeks] due to lack of response," a total of 1,184 patients (about 10% of the cohort) did just that, the authors said. Patients who stopped before 12 weeks were significantly more likely to have cirrhosis, compared with patients who persisted with therapy (adjusted odds ratio, 1.42), and also were more likely to have diabetes (AOR, 1.25) and pretreatment substance use disorder, or SUD (AOR, 1.24).

VITALS

Major Finding: Hepatitis C patients who discontinue ribavirin/pegylated interferon therapy before 12 weeks are significantly more likely to have cirrhosis (AOR, 1.42), diabetes (AOR, 1.25), or substance use disorder (AOR, 1.24), and less likely to take growth factor (AOR, 0.56), compared with patients who persist with therapy.

Data Source: A national sample of 11,019 veterans treated for genotype 1 hepatitis C virus infection within the VA health care system between 2002 and 2007.

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They were also half as likely to use growth factor as were those who continued therapy (AOR, 0.56; *P* less than .01). The growth factors included erythropoietin, darbepoetin, granulocyte colony-stimulating factor, and granulocyte macrophage colony-stimulating factor.

The authors also assessed patients who discontinued treatment between 12 and 24 weeks of therapy (including 317 patients with known early virologic response who discontinued despite their response). These patients were more likely to have pretreatment depression (AOR, 1.59), were slightly less likely to have other mental illnesses (AOR, 0.65), and – once again – were nearly half as likely to use growth factor as were patients who persisted with the therapy (AOR, 0.64).

Finally, the authors looked at patients who discontinued before 38.4 weeks. "No variables significantly predicted discontinuation in this time period in bivariate or multivariate analyses," wrote Dr. Beste of the VA Puget Sound Healthcare System, Seattle, and her coauthors.

Regarding SUD as a predictor of discontinuation, the authors wrote that "patients with history of substance abuse may benefit from early support and intervention during treatment in order to continue antiviral therapy."

Of the pretreatment depression that emerged as a predictor in the 12-24 week discontinuation group, they wrote, "Prior studies report that the depressive side effects of interferon peak by week 25, which may explain the observed association between depression and discontinuation midtreatment."

Finally, Dr. Beste and colleagues commented on the use of growth factor, which correlated with reduced risk of discontinuation both before 12 weeks and from weeks 12 to 24. They speculated that growth factor use "leads to improvement in low blood counts, allowing providers to continue treatment when otherwise it would be stopped."

Therefore, "appropriate use of growth factors should be prospectively evaluated as a modifiable means to prevent treatment discontinuation," they said. ■

Combination of Two Oral Drugs Shows Promise for Hep C

BY DENISE NAPOLI

FROM THE LANCET

A combination of two oral drugs for reducing viral load in hepatitis C patients had good safety and tolerability in a small, phase I study.

The finding points the way toward an alternative to the current standard of care – subcutaneous pegylated interferon-alfa plus oral ribavirin – which has limited tolerability and efficacy.

The novel therapies that were tested in this study are RG7128, a nucleoside polymerase inhibitor, and danoprevir, a protease inhibitor, wrote Dr. Edward J. Gane of Auckland (New Zealand) Clinical Studies Ltd., an early-phase clinical pharmacology unit, and his colleagues.

Both compounds have potent in vitro and in vivo activity against HCV, and at the time of this study, each was in phase I development, wrote the authors. Both agents are made by Roche, which funded the study.

The Interferon-Free Regimen for the Management of HCV (INFORM-1) study was a randomized, double-blind, placebo-controlled, dose-escalation trial. Eligible patients were aged 18-65 years and had been chronically infected with HCV genotype 1, with a minimum HCV RNA of 10^5 IU/mL.

Patients with cirrhosis, other hepatic or renal failure, and comorbid HIV were not included in this study – a potential limitation, the authors wrote (Lancet 2010 Oct. 15 [doi:10.1016/S0140-6736(10)61384-0]).

In all, 88 patients were randomized into seven groups to receive either placebo or various doses of the novel treatment. Most were white (90%), male (80%), and infected with genotype 1a (79%). The mean age was roughly 47 years.

Overall, 73 patients were ultimately given at least one dose of the assigned treatment and 14 received placebo.

In patients who received the highest doses of treatment (1,000 mg RG7128 twice daily plus 900 mg of danoprevir twice daily), "five of eight treatment-naive patients and two of eight [previous] null responders [to standard HCV therapy] had HCV RNA concentrations below the limit of detection (less than 15 IU/mL)," the authors wrote.

Additionally, "seven of eight treatment-naive patients and four of eight null responders had HCV RNA concentrations below the limit of quantification (43 IU/mL)."

Median reduction in HCV RNA concentrations among the treatment-naive patients was 5.1 log10 IU/mL, and among the previous null responders it was 4.9 log10 IU/mL. In comparison, the mean baseline log10 plasma HCV RNA concentration was 6.4 IU/mL.

The treatment group who received the lowest dose (500 mg RG7128 twice daily, plus 100 mg danoprevir every 8 hours) also saw a median reduction in viral load of 3.7 log10 IU/mL. Of the eight patients in this low-dose cohort, one patient achieved viral levels below the level of detection at 14 days.

"No evidence of treatment-emergent resistance to either compound was identified during the study, and 72 of 73 patients in the treatment groups had a continuous decline in viral load, which was maintained throughout dosing," they said.

At 14 days – the study's completion – patients continued therapy by switching to standard of care treatment with pegylated interferon alfa-2a and ribavirin.

"The INFORM-1 study provides proof of concept for an oral approach to the treatment of HCV, in which a combination of direct-acting antiviral drugs is safely coadministered without pegylated interferon," wrote the investigators.

Roche developed RG7128 and recently bought the worldwide development and commercialization rights to danoprevir from InterMune Inc. Several investigators, including Dr. Gane, have received grants, travel fees, advisory board fees, and other support from Roche and other drug makers; several are employees of Roche or InterMune. ■

VIEW ON THE NEWS

New Treatment Brings Hope, Questions

In an editorial accompanying the article, Dr. David L. Thomas wrote that "we are on the eve of a new era in hepatitis C virus treatment."

Indeed, he added, for the first 2 decades after the virus was discovered, "only ribavirin and interferon-alfa–related compounds were approved for HCV treatment, and nearly a decade has passed since the last substantive upgrade."

However, he pointed out some "important limitations" to early-phase trials such as this. For example, although the study met its safety objectives, "the goal of HCV treatment is to eradicate infection," an end point achieved when HCV RNA cannot be detected in blood at the end of treatment and 6 months later.

Because patients in the study rolled over to pegylated interferon-alfa and ribavirin after completion of study drug treatment, "the study will never tell us about the ultimate efficacy of the combined use of the two direct-acting agents."

Moreover, "long-term risk of viral resistance with a two-drug direct-acting regimen cannot be confidently assessed, because drug use was directly observed in a clinical trial unit, and only limited resistance testing was presented."

Even if a treatment with 100% efficacy is ultimately developed, "what is unclear at this stage is whether HCV testing and treatment will penetrate to the prisons, drug-treatment centres, and other venues where many HCV infected individuals are found and unknowingly harbour the virus," he wrote.

DAVID L. THOMAS, M.D., *is professor at Johns Hopkins University in Baltimore. This editorial was published online in the Lancet (2010 Oct. 15 [doi:10.1016/50140-6736(10)61497-3]). He has received drugs for phase IV studies with Merck & Co. and Gilead Sciences Inc., and has received an honorarium from Merck and payment for development of educational materials from companies who in turn receive support from drug companies.*