15 APRIL

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Hepatitis C Virus (HCV)–HIV Coinfection: 2b or Not 2b?

Laguno M, Cifuentes C, Murillas J, et al. Randomized trial comparing pegylated interferon α-2b versus pegylated interferon α-2a, both plus ribavirin, to treat chronic hepatitis C in human immunodeficiency virus patients. Hepatology 2009; 49:22–31.

In a randomized, multicenter, open-label clinical trial, Laguno and colleagues randomized 182 HIV-infected patients with HCV coinfection to receive, in addition to ribavirin (800–1200 mg per day), either pegylated IFN-α-2b or pegylated IFN-α-2a. Pegylated IFN-α-2b was administered to 96 patients at a dosage of 80–150 μg per week, whereas pegylated IFN-α-2a was given to 86 patients at a dosage of 180 μg per week; the planned duration of treatment was 48 weeks. Overall, 45% of infections were due to HCV genotype 1, 34% were due to genotype 3, 17% were due to genotype 4, and 3% were due to genotype 3. Fifty-nine percent of patients had a baseline serum HCV RNA level >600,000 IU/mL. The baseline $CD4^+$ lymphocyte count was >300 cells/mm^3 (mean, 598 cells/mm^3), and the plasma HIV RNA level was <200 copies/mL in 73% of patients.

An intent-to-treat analysis revealed no statistically significant difference in the proportions of patients who achieved a sustained virological response, which was defined as an undetectable serum HCV RNA level 24 weeks after the end of therapy; a sustained virological response was observed in 42% and 46% of recipients of pegylated IFN-α-2b and pegylated IFN-α-2a, respectively ($P = .6$). Among patients who were infected with genotypes 1 or 4, sustained virological response was achieved in 28% of pegylated IFN-α-2b recipients and in 32% ($P = .67$) of those assigned pegylated IFN-α-2a, whereas among persons infected with genotypes 2 or 3, sustained virological response oc-

curred in 62% and 72% ($P = .6$), respectively. Attainment of an early virological response, which was defined as a >2-$\log_{10}$ reduction in the HCV RNA level at 12 weeks, was predictive of sustained virological response (positive predictive value, 64%; negative predictive value, 100%; findings are for each treatment arm). Almost all patients experienced an adverse event. In 55% of patients, the event was considered of grade 3 or 4 severity; events of grade 3 or 4 severity were identified in 46% of pegylated IFN-α-2b recipients and 62% of those receiving pegylated IFN-α-2a ($P = .037$). Treatment discontinuation as a consequence of an adverse reaction occurred in 8% and 13% of recipients of pegylated IFN-α-2b and pegylated IFN-α-2a, respectively ($P = .47$). Leukopenia and thrombocytopenia were each more frequently encountered in patients who received pegylated IFN-α-2b.

Thus, the results of this study suggest that there is little to choose between these 2 pegylated IFNs with regard to efficacy. However, although this study was sufficiently powered to be able to detect a difference in sustained virological response >20%, the power to detect a similar difference in the patients infected with genotypes that had less favorable responses to therapy was much lower. This is of great relevance in the United States, where genotype 1 predominates. It should also be noted that, in contrast to the results discussed here, a retrospective analysis of patients who had participated in previous clinical trials found a higher rate of early virologic response in pegylated IFN-α-2a recipients than in pegylated IFN-α-2b recipients [1]. Consistent with the current data, however, that study also found a higher rate of serious adverse events among pegylated IFN-α-2a recipients.

Although IFN-α-2b and IFN-α-2a themselves have only minor differences, the 2 commercially available pegylated IFNs, pegylated IFN-α-2b and pegylated IFN-α-2a, differ significantly [2]. The former is a smaller molecule, consisting of a linear 12-kDa polyethylene glycol (PEG) attached to the 19 kDa IFN by a bond that is subject to hydrolysis, which releases the active moiety in vivo, making pegylated IFN-α-2b essentially a prodrug. In contrast, pegylated IFN-α-2a contains a 40-kDa branched PEG attached to the IFN molecule by a stable amide bond. These differences result in marked pharmacokinetic differences, with pegylated IFN-α-2b being more rapidly absorbed from its subcutaneous injection site, having a larger volume of distribution, and having more-rapid clearance. Nonetheless, the results for the HCV-HIV–coinfected patients described by Laguno and colleagues suggest that, if the 2 pegylated IFNs differ in therapeutic efficacy, the difference is not great. The results are also more or less consistent with the conclusions of a recent review that concluded that available published data do not support a firm conclusion regarding the relative efficacy of the 2 available pegylated IFNs in HIV-uninfected patients with chronic hepatitis due to HCV [3].

References

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