COINFECTION

ICAAC 2013: Interferon Response Reduces Liver Disease and Death in HIV/HCV Coinfected

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Juan Berenguer at ICAAC 2013 (Photo: Liz Highleyman)

Effective interferon-based therapy that produces sustained virological response (SVR) led to significant reductions in liver decompensation, HIV disease progression, and both overall and liver-related mortality among HIV/HCV coinfected patients, according to a presentation at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2013) last week in Denver.

Over years or decades chronic hepatitis C virus (HCV) infection can lead to severe liver disease including cirrhosis and hepatocellular carcinoma (a type of liver cancer).

People coinfected with HIV and HCV tend to experience more rapid liver disease progression and respond less well to interferon-based therapy than those with hepatitis C alone. But despite their poorer response, coinfected people stand to benefit more from treatment. HIV negative people with HCV alone are generally not treated if they have mild-to-moderate liver disease, but coinfected individuals may benefit from earlier therapy due to their risk of more aggressive disease.

Juan Berenguer from Hospital Gregorio Marañón and fellow investigators with the GESIDA 3603 HIV/HCV Cohort Study looked at the effects of successful interferon-based therapy on liver disease progression and death among HIV/HCV coinfected patients without advanced liver fibrosis at baseline.

While theclinical benefits of sustained response -- continued undetectable viral load 12 or 24 weeks after completing treatment -- for HIV/HCV coinfected patients with advanced liver disease have been well characterized, outcomes for coinfected people with mild-to-moderate liver damage are less well understood, the researchers noted as background.

This analysis included 695 participants in the GESIDA 3603 study cohort, a group of coinfected patients at 19 clinical centers in Spain who started treatment with conventional or pegylated interferon plus ribavirin between January 2000 and January 2008.

About three-quarters of participants were men, most were white, the median age was 40 years, and more than 80% had a history of injection drug use. The median CD4 T-cell count was high, at 546 cells/mm^3, but 20% had a history of AIDS (CDC Category C disease).

Two-thirds of participants had difficult-to-treat HCV genotypes 1 or 4, the rest genotypes 2 or 3. Pre-treatment biopsies showed that 11% had absent liver fibrosis (Metavir stage F0), 42% had mild fibrosis (F1), and 47% had moderate fibrosis (F2). People with bridging fibrosis (F3) or cirrhosis (F4) were not included in this analysis.

The researchers looked at various liver-related outcomes including liver decompensation (inability to perform critical functions), hepatocellular carcinoma, liver transplantation, liver-related death, and all-cause mortality. Assessments of liver damage were made using biopsies and transient elastometry (FibroScan), a non-invasive method that uses sound waves to measure liver stiffness.

Results

Overall, 35% of study participants achieved sustained virological response.
Factors significantly associated with greater likelihood of SVR included:

- HCV genotype 2 or 3 vs 1 or 4: odds ratio (OR) 4.24, or about 4 times more likely;
- Low pre-treatment HCV viral load (<500,000 IU/mL): OR 1.88, or nearly twice as likely;

- Absence of heavy alcohol use (<50 g/day): OR 4.04.

Liver stiffness scores decreased significantly more following treatment among patients who achieved SVR.
Over a median follow-up period of 59 months, event rates for people with and without SVR were as follows:

- Liver decompensation: 0.26 vs 0.84 per 100 person years (PY);
- Hepatocellular carcinoma: 0.13 vs 0 per 100 PY;
- Liver-related mortality: 0 vs 0.09 per 100 PY;
- All-cause mortality: 0.39 vs 0.63 per 100 PY;
- Progression to AIDS: 0.13 vs 0.55 per 100 PY.

Participants who achieved SVR were significantly less likely than non-responders to experience liver decompensation (1.1% vs 6.2%) and all liver-related events.
People with sustained response had significantly lower liver-related mortality (0.4% vs 2.6%) and overall mortality (1.5% vs 5.2%).
Successfully treated patients were also less likely to experience HIV disease progression to AIDS (0.7% vs 3.3%).
However, when results were broken down by pre-treatment liver disease stage, differences in outcomes (except for AIDS) remained significant only for people with moderate fibrosis (F2), not for those with absent or mild fibrosis (F0-F1).
In a multivariate analysis adjusting for sex, age, CD4 count, HIV disease stage, HCV genotype, and HCV viral load, adjusted hazard ratios for liver-related events were 0.13 overall, 0.21 for fibrosis stages F0-F1, and 0.11 for stage F2.

"Eradication of HCV in HIV/HCV coinfected patients with non-advanced liver fibrosis (F0 to F2), and, more specifically, with moderate stages of liver fibrosis (F2), is associated with a reduction in the risk of mortality and liver-related events," the researchers concluded.

"These findings constitute a strong rationale for considering anti-HCV treatment in this population group, particularly treatment based on the newer and more effective direct antiviral agents," they added.

Following the presentation Joseph Eron noted that numbers of patients with specific fibrosis stages were small, and we cannot assume treatment conferred no benefit for people with less advanced liver disease. Berenguer agreed, saying, "I think if we follow them longer, even patients with mild fibrosis would get benefits."

Berenguer and Jose Miro from the University of Barcelona, who discussed liver transplantation at the same session, both acknowledged that their presentations were largely history due to the advent of effective new direct-acting anti-HCV drugs.

Interferon/ribavirin dual therapy cures only about half of HCV genotype 1 patients -- even less among those with HIV -- with a year of difficult-to-tolerate therapy. This is curently being replaced by triple therapy with add-on HCV protease inhibitors, bringing cure rates up to around 75% even for coinfected patients. Next generation direct-acting antivirals now under study, which will first be used as interferon add-ons and eventually in all-oral regimens, promise to bring SVR rates into the 80%-100% range with shorter, better-tolerated courses of treatment.

Without the disadvantages of year-long therapy, potentially severe side effects, and often suboptimal response rates, HIV/HCV coinfected people will have more incentive to undergo treatment that reduces their long-term risk of liver failure and death.

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Reference

J Berenguer, FX Zamora, C Díez, et al. Hepatitis C eradication reduces liver decompensation, HIV progression, and death in HIV/HCV-co-infected patients with non-advanced liver fibrosis. 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2013). Denver, September 10-13, 2013. Abstract H-1527.