ANNALS of Hepatology

HEPATOLOGY HIGHLIGHTS

January-February, Vol. 11 No.1, 2012: 4-6

Hepatology Highlights

Zamil Karim,*,‡ Yi-Tzu Nancy Fu,*,‡ Eric M. Yoshida*

*Division of Gastroenterology, the University of British Columbia, Vancouver, Canada.
‡ Co-primary authors of equal significance.

Balapiravir plus peginterferon alfa-2a (40KD)/ribavirin in a randomized trial of hepatitis C genotype 1 patients

Nelson DR, et al. Hepatitis C infection is the leading cause of end stage liver disease worldwide. Standard therapy with pegylated interferon and ribavirin have resulted in suboptimal responses, particularly for genotype 1. However, the advent of new direct-acting antiviral agents against HCV have resulted in dramatically improved rates of cure of the virus.

In this issue, Nelson DR, *et al.*, report the results of a randomized double-blinded, multi-center phase IIb clinical trial studying the efficacy, optimal treatment regimen, and safety of balapiravir, a nucleoside analogue inhibitor of HCV RNA dependent RNA polymerase. This study evaluated 516 treatment naive, chronic HCV mono-infected patients. All patients had HCV genotype 1 and were between the ages of 18-65 years. Patients were randomized to one of seven treatment groups in which they received different dosing combinations of balapiravir, pegylated interferon and ribavirin. HCV RNA counts were followed to assess for early and sustained virological suppression. While all patients demonstrated dose dependent reductions in serum HCV RNA levels, the study protocol was amended early, with discontinuation of the balapiravir arm with the highest dose and a reduction in duration from a planned 24 week to 12 weeks of balapiravir exposure in the other arms. This was due to the high incidence of serious adverse events attributed to balapiravir, including significant lymphopenia ($< 0.5 \times 10^9$), ocular adverse events, infections, and death in three patients attributed to study drug (varicella infection, lymphoma and suicide). The severe lymphopenia recovered in "most" of the patients although recovery was slow, taking up to one year post-treatment in some cases. The protocol dose amendments resulted in a relatively low sustained virologic response (SVR) of 29-50% compared to 43% for the peginterferon and ribavirin control arm. The significant toxicity especially the lymphopenia was surprising as it had not been reported in previous clinical trials. The adverse effect profile of the clinical trial resulted in the manufacturer (Hoffman La Roche) curtailing further drug development with balapiravir.

This study showed that while the addition of balapiravir to pegylated interferon and ribavirin may have increased the rate HCV RNA suppression, the significant rate of serious drug related adverse events required dose modifications and discontinuations resulting in no overall difference in rates of sustained virological response with the addition of this drug. Although the significant adverse effects are not thought to be a class effect of HCV nucleoside polymerase inhibitors, this remains to be seen. This negative trial is of significant value as a reminder to both the hepatology community and pharmaceutical industry to be vigilant of the adverse events of new agents being released in this field.

Correspondence and reprint request:
Eric M. Yoshida MD, MHSc, FRCP(C), FACP, FACG
Professor of Medicine, Head. Division of Gastroenterology. University of British Columbia, Canada. Vancouver General Hospital. Diamond Health Care Centre 5153-2775 Laurel Street, Vancouver, BC, V5Z 1M9, Canada. Tel.: 604-875-5371. Fax: 604-875-5447.

Re-treatment of previous non-responders and relapsers to interferon plus ribavirin with peginterferon alfa-2a (40KD), ribavirin ± amantadine in patients with chronic hepatitis C: randomized multicentre clinical trial

Pessôa MG, *et al.* Chronic hepatitis C infection (CHC) often leads to multitudes of long-term complications. Eradication of CHC with sustained virological response (SVR) can be achieved with combination therapy of peginterferon (alpha-2a or alpha-2b) and ribavirin. There were conflicting reports on the use of amantadine in CHC treatment.

In a randomized, open-label study, Pessôa, *et al.* evaluated the efficacy of 200 mg/day amantadine in addition to dual therapy of 48 weeks of 180 μg/week subcutaneous peginterferon alpha-2a plus 1,000/1,200 mg/day ribavirin in previous treatment non-responders or relapsers. The 182 study patients were mostly Caucasian male with predominantly genotype 1 in previous non-responders and genotype 3 in relapsers. Sixty eight patients prematurely withdrew from the study and 56 of these were due to insufficient response.

In both non-responders and relapsers, no statistically significant differences were found in SVR, biochemical response, early virological response, and complete early virological response. Interestingly, among previous non-responders, 30.8% of those received dual therapy and 22.6% of those received triple therapy reached SVR. On the other hand, among previous relapsers, 60.5% of dual therapy patients and 56.4% of triple therapy patients reached SVR. Overall, patients had a lower rate of SVR if they were randomized to triple therapy (37%) compared to dual therapy (43.3%).

This study demonstrated that a substantial proportion of CHC in previous non-responders and relapsers can be eradicated with retreatment. Amantadine, however, did not augment the efficacy of combination therapy in previous non-responders and relapsers. In the previous decade, much had been speculated about amantadine's efficacy in HCV treatment. This paper should be the final nail in the coffin regarding amanatidine in HCV. The final verdict: triple therapy with amantadine for treatment of CHC should be discouraged.

Causes of renal failure in patients with decompensated cirrhosis and its impact in hospital mortality

Carvalho GC, et al. Renal failure is a major cause of morbidity and mortality in hospitalized patients with end stage liver disease. The cause of renal failure is often multifactorial, and can include hypovolemia, hepatorenal syndrome, parenchymal renal disease, and obstructive causes.

In this issue, Carvalho, *et al.* report the findings of a retrospective study involving 406 patients with decompensated cirrhosis, admitted to a tertiary care hospital in Bahia, Brazil from January 2005 to December 2007. The study examines the incidence, etiology and overall outcomes of renal failure in these patients. They documented renal failure, defined as serum creatinine > 1.5 mg/dL (> 114 μmol/L), in 39% of patients on admission. Furthermore, 10% of subjects developed renal failure during their hospitalization. The investigators found a significantly higher mortality associated with renal failure. They also found the most common causes to be hypovolumia and bacterial infections, whereas hepatorenal syndrome and bacterial infections were associated with the highest mortality. This study highlights the magnitude of the problem of renal disease in patients hospitalized with cirrhosis, and speaks to the importance of prevention and increased vigilance of this problem.

Serum lipids and chronic hepatitis C genotype 4: interaction and significance

Khattab MA, *et al.* Hepatitis C virus (HCV) can interact with host's lipid and glucose metabolism leading to steatosis and insulin resistance (IR). Previous studies have demonstrated genotype-specific mechanisms. However, what still remains unknown is the association between these metabolic derangements with liver histology and viral load in HCV genotype 4 (HCV4) patients.

In a prospective, control-matched study, Khattab, *et al.* compared the metabolic profiles, HCV RNA levels and liver histology between 183 HCV4 infected patients and 106 healthy controls. Significantly higher levels of insulin, CRP and homeostasis model assessment of IR index (HOMA-IR) were noted in the HCV4 cohort. However, they had a favourable lipid profile with significantly lower TG, LDL-C and higher HDL-C. Greater steatosis was positively associated with BMI and HOMA-IR but negatively associated with serum adiponectin level. Age, BMI and HOMA-IR independently predicted grades of portal/periportal inflammation. HOMA-IR, portal/periportal inflammation grade, serum cholesterol and age independently predicted the severity of fibrosis. Higher HCV RNA levels were significantly associated with severe hepatitis activity, milder hepatic fibrosis, and TG levels.

This study showed that HCV4 steatosis was associated with patients with metabolic syndrome which lead to further progression of liver disease and hypolipidemia. These findings strengthened the hypothesis that HCV infection can directly link to lipid metabolism and a possible role of lipid factors in the HCV4 life cycle.