Hepatitis Research Review™

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In this issue:

Abbreviations used in this issue:

DAA = direct-acting antiviral; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus; **HCC** = hepatocellular carcinoma; **HCV** = hepatitis C virus; **IFN** = interferon; **LRD** = liver-related death; **LT** = liver transplantation; **SVR12** = sustained virological response at 12 weeks after end of therapy; **Tregs** = T regulatory cells.

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Welcome to issue 45 of Hepatitis Research Review.

Several studies in this issue attest to the benefits of direct-acting antiviral agents (DAAs). In a cost-effectiveness analysis, pre-transplant DAA treatment proved to be more cost-effective for both decompensated cirrhosis and complicating hepatocellular carcinoma groups. In an investigation of the real-world efficacy of DAA therapy in chronic HCV patients with complicating HCC, in non-liver transplanted and transplanted patients, DAA therapy in the post-transplant setting resulted in a high rate of cure, which suggests that DAAs may reasonably be deferred until then in HCV patients in whom HCC, rather than critical hepatic functional decompensation, is the primary reason for transplantation. In another study, DAA therapy was found to be highly effective in reversing cryoglobulinaemic vasculitis related to chronic HCV infection.

I hope you enjoy the selection in this issue and I welcome your comments and feedback.

Kind Regards,

Professor Stephen Riordan

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Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: a systematic review and meta-analysis

Authors: Chen G et al.

Summary: The aim of this systematic review and meta-analysis was to provide an updated estimate of the efficacy and safety of anti-HCV treatment (interferon [IFN]-based therapy versus IFN-free pan-oral direct-acting antiviral agents [DAAs]) in patients with chronic HCV coinfected with HBV (overt versus occult). Thirty-six studies (1185 HBV/HCV-coinfected patients) were included in the review; 29 studies (1037 coinfected patients) involved 24–48 weeks of IFN-based therapy and 7 (148 coinfected patients) involved 8–12 weeks of treatment with DAAs.

Comment: As may occur following IFN-based treatment, instances of reactivation of HBV have been reported in chronic HBV- and HCV-coinfected patients treated with anti-HCV DAAs. This phenomenon has prompted recommendations from the American Association for the Study of Liver Diseases, the Infectious Diseases Society of America and the European Association for the Study of the Liver that all patients with chronic HCV infection be screened for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb) prior to the initiation of anti-HCV DAA treatment. This systematic review and meta-analysis aimed to provide an updated assessment of risk of HBV reactivation related to anti-HCV treatments in HBV-HCV coinfected patients. In HBsAg-positive patients, the HBV reactivation rate, based on a variably defined increase in circulating HBV DNA level compared to baseline, related to IFN-based treatment (14.5%) was found to be similar to that related to DAA therapy (12.2%). However, HBV reactivation occurred much earlier with DAA therapy (mostly within 4 to 12 weeks of commencing treatment) than with IFN-based therapy (mostly after the completion of treatment). In HCV patients with occult HBV coinfection (HBsAg-negative but detectable HBV DNA at baseline), no instances of HBV reactivation were documented in association with IFN-based treatment. Conversely, three case reports have reported reactivation of occult HBV infection following DAA therapy, with occurrences unrelated to the magnitude of baseline HBV levels.

Reference: Hepatology. 2017;66(1):13-26

Abstract

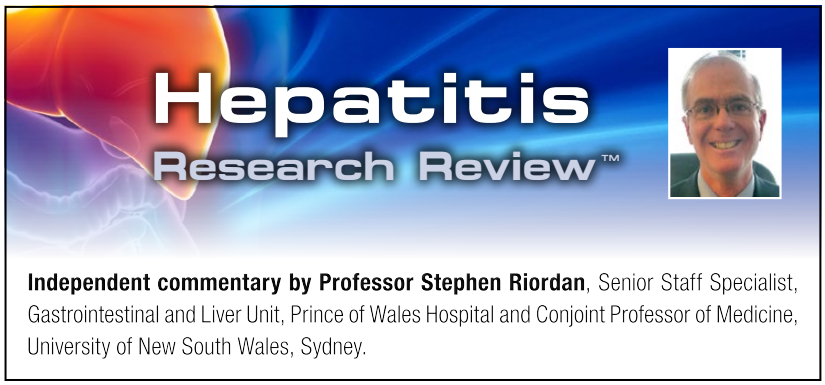
Evaluation of hepatitis B reactivation among 62,920 veterans treated with oral hepatitis C antivirals

Authors: Belperio PS et al.

Summary: This retrospective evaluation included 62,290 HCV-infected veterans completing oral DAA treatment. HBV reactivation was defined as a >1000 IU/mL increase in HBV DNA or HBsAg detection in a person who was previously negative. HBsAg testing prior to DAA treatment was conducted in 85.5% of the veterans; 0.70% were positive. Of the 84.6% tested for HBsAbs, 42.2% were positive. Of the entire cohort, 9 patients had evidence of HBV reactivation occurring while on DAA treatment; 8 cases were patients known to be HBsAg-positive, and 1 was a patient known to be isolated HBcAb-positive. Seventeen other patients had small increases in HBV DNA levels that did not qualify as HBV reactivation. Only 3 of the 9 patients identified with HBV reactivation in this cohort exhibited peak alanine aminotransferase elevations >2 times the upper limit of normal.

Comment: This study is another to examine the risk of HBV reactivation in coinfected HBV-HCV patients undergoing DAA treatments, this time as a retrospective analysis using the US Department of Veteran's Affairs database. The observed incidence of HBV reactivation in HBsAg-positive patients was 8.3%, with an incidence of biochemical hepatitis of 2.4%. Most instances of reactivation were associated with only a modest increase in HBV DNA replication and unaccompanied by an elevation in serum alanine aminotransferase level. Importantly, risk of HBV reactivation was not related to baseline HBV DNA levels, with HBV DNA being undetectable in 38% of those in whom HBV reactivation subsequently occurred. Risk of reactivation in HBsAg-negative patients with a positive hepatitis B core antibody result at baseline was substantially lower (0.58%).

Reference: Hepatology. 2017;66(1):27-36
Abstract



Independent commentary by Professor Stephen Riordan, Senior Staff Specialist, Gastrointestinal and Liver Unit, Prince of Wales Hospital and Conjoint Professor of Medicine, University of New South Wales, Sydney.

Risk of end-stage liver disease, hepatocellular carcinoma, and liver-related death by fibrosis stage in the hepatitis C Alaska Cohort

Authors: Bruden DJT et al.

Summary: This analysis included 407 American Indian/Alaska Native persons with HCV infection and no/mild (Ishak = 0–1; n=150), moderate (Ishak = 2; n=131), or severe (Ishak = 3–4; n=88) fibrosis or cirrhosis (Ishak = 5–6; n=38). All were followed-up from liver biopsy to the development of end-stage liver disease (ESLD), hepatocellular carcinoma (HCC), and liver-related death (LRD) according to fibrosis stage. The average time of follow-up was 7.3 years. Within 5 years of biopsy, 1.7% of persons with no/mild fibrosis developed ESLD compared with 7.9%, 16.4% and 49.0% with moderate, severe fibrosis, and cirrhosis, respectively ($p<0.01$). The 5-year outcome of HCC was 1.0%, 1.0%, 1.1%, and 13.4% among persons with no/mild fibrosis, moderate fibrosis, severe fibrosis, and cirrhosis, respectively ($p<0.01$). Five years after biopsy, 0.0% of persons with no/mild fibrosis had died of a LRD compared with 1.0% of persons with moderate fibrosis, 4.7% with severe fibrosis, and 16.3% with cirrhosis ($p<0.01$).

Comment: This large, prospective, population-based cohort study investigated the incidences of three adverse outcomes of chronic HCV infection, namely, hepatic decompensation, HCC and LRD, during the first 5 years of follow-up after liver biopsy. Under 2% of patients with no or minimal hepatic fibrosis developed hepatic decompensation or HCC and no such patient died of a LRD during this time. By 10 years, however, over 8% of this group had developed hepatic decompensation. At the other end of the histological spectrum, around 50% of patients with compensated cirrhosis at baseline developed decompensation over 5 years, while 13.4% developed HCC and 16% died of a LRD. Persons with moderate hepatic fibrosis (Ishak stage 2) were at intermediate risk for complications over 5 years, with 8% developing decompensation, 1% developing HCC and 1% dying of a LRD. Risk of HCC over 5 years was over 13-fold increased in patients with established cirrhosis compared with lesser histological stages (13.4% versus 1%, respectively), highlighting the imperative for careful surveillance for HCC in those in whom cirrhosis has developed. Now that highly efficacious and generally well-tolerated DAA therapies are available, the findings otherwise serve as a timely reminder that all patients with chronic HCV infection should be considered for therapy in order to interrupt disease progression.

Reference: Hepatology. 2017;66(1):37-45
Abstract

Treatment of patients waitlisted for liver transplant with all-oral direct-acting antivirals is a cost-effective treatment strategy in the United States

Authors: Ahmed A et al.

Summary: These US researchers constructed decision-analytic Markov models representing the natural disease progression of HCV in HCC patients and decompensated cirrhosis (DCC) patients waitlisted for liver transplant (LT). The model followed hypothetical cohorts of 1000 patients (mean age 50 years) over a 30-year time horizon from a third-party US payer perspective and estimated their health and cost outcomes based on pre-LT versus post-LT treatment with an all-oral DAA regimen. For the HCC cohort, pre-LT treatment yielded 11.48 per-patient quality-adjusted life years and $365,948 per patient lifetime costs versus 10.39 and $283,696, respectively, with post-LT treatment. For the DCC cohort, pre-LT treatment resulted in 9.27 per-patient quality-adjusted life years and $304,800 per patient lifetime costs versus 8.7 and $283,789, respectively, with post-LT therapy. According to this analysis, pre-LT treatment was the most cost-effective in both populations with an incremental cost-effectiveness ratio of $74,255 (HCC) and $36,583 (DCC).

Comment: DAA treatment of chronic HCV infection in waitlisted patients with decompensated cirrhosis or complicating HCC in the pre-liver transplant setting has been shown to be of clinical benefit, in both clinical trial and real-world settings. However, only limited data are available regarding the possible economic value of such an approach, compared to deferring DAA treatment until after liver transplantation. This study developed decision-analytic, cost utility Markov models to assess the cost-effectiveness of treatment before or after liver transplantation, given the current paucity of prospective data. The results suggest that pre-transplant DAA treatment is the more cost-effective strategy for both decompensated cirrhosis and complicating HCC groups. Effective DAA treatment of patients with a baseline Model for End-Stage Liver Disease (MELD) score ≥15 results in a lower likelihood of transplantation. In those who continue to require transplantation despite a sustained virological response (SVR), viral clearance would preclude the use of an HCV-positive liver graft. The relative importance of this scenario in adversely influencing the likelihood of timely transplantation was not specifically addressed in this analysis and will need to be assessed in future studies.

Reference: Hepatology. 2017;66(1):46-56
Abstract

Immune phenotype and function of natural killer and T cells in chronic hepatitis C patients who received a single dose of anti-microRNA-122, RG-101

Authors: Stelma F et al.

Summary: Immunological analyses are reported for 32 patients with chronic HCV genotype 1, 3, or 4 infection treated with a single subcutaneous administration of placebo (n=4) or RG-101 at 2 mg/kg (n=14) or 4 mg/kg (n=14). HCV RNA decreased in all RG-101 recipients (mean decline at week 2, 3.27 $\log_{10}$ IU/mL) and was undetectable in 15 patients at week 8. In addition, plasma IFN-γ-induced protein 10 levels decreased significantly, natural killer (NK) cell proportions increased, expression of NK cell-activation receptors normalised, and NK cell IFN-γ production significantly decreased. Functional HCV-specific IFN-γ T cell responses did not change significantly in RG-101-treated patients who had undetectable HCV RNA levels by week 8. No increase in the magnitude of HCV-specific T cell responses was observed at later time points, including 3 patients who were HCV RNA-negative 76 weeks postdosing.

Comment: The host factor, microRNA-122 (miR-122), is a liver-specific microRNA that regulates cholesterol and fatty acid synthesis and has been shown to bind to the HCV genome, resulting in the promotion of viral replication. The *N*-acetylgalactosamine-conjugated anti-miR-122 antisense oligonucleotide, RG-101, inhibits HCV replication, although its precise mechanism of HCV inhibition is unclear. This randomised, double-blind, placebo-controlled, phase 1b study assessed whether RG-101 influences antiviral immunity in chronic HCV infection and whether any restoration of impaired immune function may contribute to the antiviral effect of this molecule. RG-101 exposure resulted in a reduction in HCV RNA levels and a corresponding reduction in interferon-γ-induced protein levels, an increase in NK cell proportions and normalisation of NK cell phenotype. By contrast, no restoration of *ex vivo* HCV-specific T cell function occurred, suggesting that beneficial effects on NK cells but not HCV-specific T cells likely contribute to the antiviral potential of miR-122 inhibition in patients with chronic HCV infection.

Reference: Hepatology. 2017;66(1):57-68
Abstract

Low hepatitis B virus-specific T-cell response in males correlates with high regulatory T-cell numbers in murine models

Authors: Kosinska AD et al.

Summary: The impact of gender on HBV-specific immune responses was examined in two different mouse models representing transient and persistent hepadnaviral infection; hydrodynamic injection with the HBV genome mimicked acute HBV infection, while the efficacy of therapeutic vaccination was studied in woodchuck hepatitis virus transgenic mice immunised with a DNA prime-recombinant adenovirus boost vaccination protocol. Significantly higher HBV DNA and protein levels were detected in males versus females. In the acute HBV infection model, male and female mice had similar numbers of intrahepatic HBV-specific cluster of differentiation 8-positive ($CD8^+$) T cells, but their functionality was significantly reduced in males and correlated with higher numbers of intrahepatic regulatory T cells (Tregs). Similar effects were observed in the therapeutic vaccination model, with male mice showing functionally suppressed woodchuck hepatitis virus-specific $CD8^+$ T-cell responses in the liver and significantly higher numbers of intrahepatic Tregs compared with females. Blockade of Treg responses in male mice led to augmented effector functions of specific $CD8^+$ T cells and subsequently improved virus control in both models of transient and persistent hepadnaviral infection.

Comment: Gender is a major factor influencing the outcome and severity of HBV infection, with men more likely than women to become chronic carriers after HBV exposure, to have higher circulating HBV DNA levels and to be at increased risk of HCC complicating HBV infection. Here, the authors demonstrate that gender significantly influences hepadnaviral replication and immune control in murine models of both transient and persistent hepadnaviral infection. The key finding is that the magnitude of HBV-specific $CD8^+$ T cell responses was inversely correlated with both hepadnaviral replication and protein levels and the number of intrahepatic Tregs. Enhanced induction of intrahepatic Tregs in males consequent to increased hepadnaviral replication may at least contribute to the gender-related differences in the natural history of HBV infection. The findings raise the possibility that functional blockade of Tregs, leading to enhanced HBV-specific T cell responses, may neutralise gender-related differences in HBV control.

Reference: Hepatology. 2017;66(1):69-83
Abstract

Effectiveness of hepatitis C antiviral treatment in a USA cohort of veteran patients with hepatocellular carcinoma

Authors: Beste LA et al.

Summary: This analysis included patients with HCV infection and a history of HCC who initiated DAA treatment in the national Veterans Affairs health care system. Regimens included sofosbuvir, ledipasvir/sofosbuvir, and paritaprevir/ritonavir/ombitasvir and dasabuvir with or without ribavirin. In the entire cohort of 17,487 patients, 624 patients were diagnosed with HCC prior to first DAA prescription. The HCC cohort was divided into those who received LT (HCC/LT group; n=142) prior to antiviral treatment and those treated with other modalities prior to antiviral therapy (HCC group; n=482). Overall SVR was 91.1% in non-HCC, 74.4% in HCC, and 94.0% in HCC/LT. Among HCC patients, genotype 1 had the highest SVR overall (79.1% in HCC and 96.4% in HCC/LT), and genotype 3 the lowest (47.0% in HCC and 88.9% in HCC/LT). After adjusting for confounders, the presence of HCC was associated with lower likelihood of SVR overall (adjusted OR 0.38; 95% CI, 0.29 to 0.48; p<0.001).

Comment: This observational study utilising the large Department of Veterans Affairs health care system database in the United States was performed to investigate the real-world efficacy of DAA therapy in chronic HCV patients with complicating HCC, in non-liver transplanted and transplanted patients. SVR was found to be 74.4% in 426 non-transplanted HCC patients, significantly lower than that in non-transplanted patients without HCC (91.1%). By contrast, SVR was substantially higher (94%) in 133 additional HCC patients who underwent liver transplantation following HCC diagnosis and received DAA treatment in the post-transplant setting. Reasons for the poorer antiviral treatment outcome in HCC patients prior to transplant are likely multifactorial and could relate to the distorted liver architecture and cytokine and chemokine milieus operative in a cirrhotic liver. The high rate of cure achieved post-transplant suggests that DAA therapy may reasonably be deferred until then in the subgroup of HCV patients in whom HCC, rather than critical hepatic functional decompensation, is the primary reason for transplantation.

Reference: J Hepatol. 2017;67(1):32-9
Abstract

Hepatic decompensation is the major driver of death in HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma

Authors: Cabibbo G et al.

Summary: This Italian investigation recruited 328 patients with HCV-related cirrhosis and Barcelona Clinic Liver Cancer (BCLC) stage 0/A HCC who had complete radiological response after curative resection or thermal ablation.

Comment: Liver-related prognosis in patients with HCV-associated cirrhosis and successfully treated early-stage HCC depends on two key parameters, namely, HCC recurrence and hepatic functional decompensation. In this study, a survival analysis was performed by means of a time-dependent Cox model in a large cohort of such patients, mostly Child-Pugh class A, with the aim of estimating the relative importance of HCC recurrence and hepatic functional decompensation within 12 months of complete radiological response on 5-year survival. The main factor influencing this was found to be an episode of functional decompensation within the first year, which increased mortality risk by around 7.5 times, while early HCC recurrence increased risk by around 2.5 times and the presence of oesophageal varices and older age at baseline were additional risk factors for poor 5-year survival. In the subgroup of patients with the most favourable prognostic features (no hepatic functional decompensation or HCC recurrence within 12 months and no oesophageal varices at baseline), the estimated 5-year mortality rate was 22%. By contrast, an episode of hepatic functional decompensation within 12 months in a patient with oesophageal varices was estimated to portend a 5-year mortality rate of 96%. The findings point to the importance of DAA therapy to prevent progression of cirrhosis and hepatic functional decompensation and thereby improve 5-year survival in initially well-compensated patients with HCV-associated cirrhosis and effectively managed early HCC.

Reference: J Hepatol. 2017;67(1):65-71
Abstract

Efficacy and safety of sofosbuvir plus daclatasvir for treatment of HCV-associated cryoglobulinemia vasculitis

Authors: Saadoun D et al.

Summary: This study administered an all-oral, IFN- and ribavirin-free regimen of sofosbuvir plus daclatasvir to 41 patients (median age 56 years) with active HCV-associated cryoglobulinaemia vasculitis. Treatment consisted of sofosbuvir (400 mg/day) plus daclatasvir (60 mg/day) for 12 weeks (n=32) or 24 weeks (n=9). After a median 12 weeks of therapy, 37 patients (90.2%) had a complete clinical response (i.e. improvement of all the affected organs involved at baseline and no clinical relapse); all achieved SVR12. At week 36, mean cryoglobulin level decreased from 0.56 g/L at baseline to 0.21 g/L; no cryoglobulin was detected in 50% of patients at this time point. After antiviral therapy, patients had increased numbers of Tregs, IgM$^+$CD21$^-$/low-memory B cells, CD4$^+$CXCR5$^+$ interleukin 21$^+$ cells, and T-helper 17 cells, compared with baseline levels. After a median 26 months of follow-up, no patients had a serious adverse event or relapse of vasculitis.

Comment: Circulating cryoglobulins are evident in up to 60% of patients with chronic HCV infection, while cryoglobulinaemic vasculitis occurs in around 15%. Clinical remission is closely associated with viral clearance. This open-label study assessed the efficacy of individually tailored combination sofosbuvir and daclatasvir for 12 or 24 weeks for this disorder. At week 24, 90% of patients were complete clinical responders, related to SVR. Less than 5% of patients required immunosuppressive rituximab and glucocorticoid therapy in addition to antiviral therapy. The findings point to the high efficacy of effective DAA therapy in reversing cryoglobulinaemic vasculitis related to chronic HCV infection.

Reference: Gastroenterology. 2017;153(1):49-52
Abstract

Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials

Authors: Jacobson IM et al.

Summary: Outcomes are reported from two phase 3, open-label trials (POLARIS-2 and POLARIS-3), in which patients with HCV infection who had not previously received DAA therapy were administered sofosbuvir-velpatasvir-voxilaprevir for 8 weeks or sofosbuvir-velpatasvir for 12 weeks. POLARIS-2 enrolled patients infected with all HCV genotypes with or without cirrhosis, except patients with genotype 3 and cirrhosis, and was designed to test the noninferiority of 8 weeks of sofosbuvir-velpatasvir-voxilaprevir to 12 weeks of sofosbuvir-velpatasvir using a noninferiority margin of 5%. POLARIS-3 enrolled patients infected with HCV genotype 3 who had cirrhosis, and compared rates of SVR in both groups with a performance goal of 83%.

Comment: These two phase 3, multicentre trials were designed to determine efficacy and safety of fixed-dose triple therapy using sofosbuvir (HCV NS5B inhibitor), velpatasvir (HCV NS5A inhibitor) and voxilaprevir (HCV NS3/4A inhibitor) for 8 weeks compared to 12 weeks of dual sofosbuvir and velpatasvir treatment in patients with and without HCV-associated cirrhosis not previously managed with DAA therapy. In an analysis excluding genotype 3-infected cirrhotic patients, the SVR of 95% associated with triple therapy for 8 weeks was not shown to be non-inferior to dual sofosbuvir and velpatasvir treatment for 12 weeks (98%). In a separate analysis of genotype 3-infected cirrhotic patients, identical SVR rates of 96% were found for the two treatment regimens. The addition of voxilaprevir was associated with an increased incidence of gastrointestinal side effects, such as nausea and diarrhoea, although these did not necessitate treatment cessation. It is unlikely that 8 weeks of triple sofosbuvir, velpatasvir and voxilaprevir therapy will replace 12 weeks of dual sofosbuvir and velpatasvir therapy, especially in non-genotype 3 HCV-associated cirrhotic patients.

Reference: Gastroenterology. 2017;153(1):113-22
Abstract

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