Welcome to issue 19 of Hepatitis Research Review.

One of the papers selected for this issue reports promising findings for the all-oral combination regimen of simeprevir and sofosbuvir in a population of patients with chronic hepatitis C virus 1a and Child’s grade A cirrhosis, including both treatment-naïve and prior null responders to pegylated interferon and ribavirin. Overall, 93% of patients treated with simeprevir and sofosbuvir achieved a sustained virological response at 12 weeks, compared with 75% of those treated with pegylated interferon plus ribavirin and sofosbuvir. Moreover, simeprevir/sofosbuvir was associated with a lower virological relapse rate and was better tolerated in terms of patient-reported outcomes and adverse events, compared with the interferon-containing regimen.

The last study in this issue is a critical examination of the evidence that virus-specific factors underlie the development of fulminant hepatitis following hepatitis E virus (HEV) infection. The re-analysis failed to support these reported associations. Instead, the study researchers suggest that patient-specific factors may be associated with fulminant hepatitis.

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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**All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study**

**Authors:** Nelson DR et al.

**Summary:** In this study, 101 treatment-naïve and 51 treatment-experienced patients with hepatitis C virus (HCV) genotype 3 infection received daclatasvir 60 mg plus sofosbuvir 400 mg once daily for 12 weeks. Patients with cirrhosis were permitted; the study enrolled 32 patients with cirrhosis and 109 without cirrhosis. Co-primary endpoints were the proportions of treatment-naïve and treatment-experienced patients achieving a sustained virological response (SVR) at post-treatment week 12 (SVR12). SVR12 rates were 90% and 86% in treatment-naïve and treatment-experienced patients, respectively; no virological breakthroughs occurred, and ≥99% of patients had a virological response at the end of treatment. SVR12 rates were higher in the non-cirrhotic cohort (96%) than in the cirrhotic cohort (63%).

Five of 7 patients who previously failed treatment with a sofosbuvir-containing regimen and 2 of 2 who previously failed treatment with an alisporivir-containing regimen achieved SVR12. Virological outcomes were unaffected by baseline characteristics, including gender, age, HCV-RNA levels, and interleukin (IL)-28B genotype. The treatment regime was well tolerated; there were no adverse events (AEs) leading to discontinuation and no serious treatment-related AEs. There was a low rate of grade 3/4 laboratory abnormalities; all were transient.

**Comment:** In this phase III study, the efficacy and safety of a 12-week, ribavirin-free course of combination daclatasvir and sofosbuvir were investigated in both pegylated interferon-based treatment-naïve and treatment-experienced subgroups of patients with chronic genotype 3 HCV infection. In non-cirrhotic patients, SVR12 rates were 97% and 94% in treatment-naïve and treatment-experienced subgroups, respectively. In cirrhotic patients, SVR12 rates were 58% and 63% in these two subgroups. Treatment was well tolerated in all subgroups. The findings demonstrate high rates of antiviral efficacy, despite a relatively short duration of treatment and in the absence of concurrent ribavirin therapy, in non-cirrhotic chronic genotype 3 HCV patients, including those who failed prior pegylated-interferon-based treatment. There remains a need to identify strategies that optimise treatment efficacy in patients with cirrhosis.

**Reference:** Hepatology. 2015;61(4):1127-35

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**Abbreviations used in this issue:**

- GT = genotype; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HEV = hepatitis E virus; HCV = hepatitis C virus; SVR = sustained virological response

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Long-term effect of HCV eradication in patients with mixed cryoglobulinaemia: a prospective, controlled, open-label, cohort study

Authors: Gragnani L et al.

Summary: These researchers examined the effects of interferon-based therapy on HCV patients with and without mixed cryoglobulinaemia (MC), with and without symptoms. The study also evaluated the long-term effects of HCV eradication on MC. Patients with HCV were assigned to 1 of 3 groups: MC syndrome (MCS)-HCV (121 patients with symptomatic MC), MC-HCV (132 patients with asymptomatic MC), and HCV (158 patients without MC). Pegylated interferon plus ribavirin were given as standard protocols. Patients were followed-up after treatment for a mean 92.5 months. A significant difference was observed in the rate of SVR between the HCV group and both the MC-HCV (p=0.009) and MC-HCV+MCS-HCV (p=0.014) groups. Multivariate logistic regression analysis identified cryoglobulinaemia as an independent prognostic factor of nonresponse. The clinical-immunological response in MCS-HCV correlated with the virological one. All SVR patients also achieved a sustained complete or partial clinical response. SVR was associated with the disappearance of all MCS symptoms in the majority of patients (57%); definite MCS persisted in only 3%.

Comment: Mixed cryoglobulinaemia (MC) is a lymphoproliferative disorder mostly associated with HCV infection. Circulating cryoglobulins are evident in around 40% to 60% of patients with HCV infection, while up to 5% of HCV-infected patients have symptomatic MC. Here, the authors prospectively evaluated in a large cohort of HCV-infected subjects both the long-term effects of HCV eradication on MC and whether the presence of MC influences the antiviral efficacy of pegylated interferon/ribavirin therapy. The findings demonstrate that a substantial majority of patients in whom SVR is achieved also experience remission of MC, while persistent remission of MC does not occur in the majority of patients in whom SVR is achieved. Interestingly, cryoglobulinaemia was identified as an independent indicator of non-response to pegylated interferon/ribavirin treatment. An explanation for the latter observation remains to be proven, but may relate to sequestration of HCV in lymphatic reservoirs.


PCSK9, apolipoprotein E and lipoviral particles in chronic hepatitis C genotype 3: Evidence for genotype-specific regulation of lipoprotein metabolism

Authors: Bridge SH et al.

Summary: Lipoviral particle (LVP) and proprotein convertase subtilisin kexin type 9 (PCSK9) concentrations were measured in 51 patients with HCV GT3 compared with HCV GT1, to indirectly examine the role of the LDL receptor (LDLR) in LVP clearance. In the HCV GT3 cohort, LVP load was negatively correlated to PCSK9, apolipoprotein E (apoE) (r = -0.421; p=0.008) and apolipoprotein E (apoE) (r = -0.428; p=0.013). The LVP ratio (LVP/LVP+/LVP-vari) varied more than 35-fold (median 0.280); PCSK9 was the strongest negative predictor of LVP load, with a negative correlation (R = -0.428; p=0.013). The homeostasis model assessment of insulin resistance (HOMA-IR) was not associated with LVP load or LVP+. PCSK9 concentrations were significantly lower in HCV GT3 compared with HCV GT1 (p<0.001). No correlation was seen between PCSK9 and LDL cholesterol in either HCV cohort.

Comment: Recent data point to an important association between HCV and lipoproteins. This is the first study to quantify plasma LVPs in patients with chronic genotype 3 HCV infection and to compare associations to those previously documented in genotype 1 HCV infection. Notably, the study found that the plasma LDL cholesterol was depleted by low density lipoprotein receptor-mediated uptake of LVP as an important mechanism by which entry of this genotype to hepatocytes occurs.

Reference: J Hepatol. 2015;62(4):763-70

Hepatitis C virus-induced reduction in miR-181a impairs CD4+ T-cell responses through overexpression of DUSP6

Authors: Li GY et al.

Summary: This article describes a significant decline of microRNA (miR)-181a expression and overexpression of dual specific phosphatase 6 (DUSP6) in CD4+ T cells from patients with chronic HCV compared with CD4+ T cells from healthy controls. A negative association was observed between the levels of miR-181a and levels of DUSP6 overexpression. Reconstitution of miR-181a or blockade of DUSP6 expression in CD4+ T cells led to improved T cell responses including enhanced CD25 and CD69 expression, increased IL-2 expression, and improved proliferation of CD4+ T cells in the chronic HCV cohort.

Comment: T cell function is crucial to viral clearance or persistence. However, the precise mechanisms controlling T cell responses during viral infection are largely unknown. MicroRNAs (miR) are 12- to 23-nucleotide RNA molecules that regulate gene expression via post-transcriptional repression or target messenger RNA degradation. This study provides preliminary evidence that miR-181a and DUSP6, a cytoplasmic phosphatase that inactivates T cell receptor signalling and a signature marker of T cell senescence, are used by HCV to diminish T cell responses. In particular, an HCV-induced reduction in miR-181a expression was demonstrated that impaired CD4+ T cell activity via an up-regulation of DUSP6 expression, thus representing a novel mechanism favouring HCV persistence. Targeted inhibition of DUSP6 may represent a future treatment strategy.


Abstract
Hepatitis C virus infection inhibits P-body granule formation in human livers

Authors: Pérez-Villaró G et al.

Summary: These researchers have previously detailed how HCV infection disrupts the formation of P-bodies in cell culture. The aim of this investigation was to determine whether P-body disruption also occurs in vivo. Formalin-fixed paraffin-embedded liver biopsy specimens from healthy donors, patients with non-virus-related liver inflammation, HCV- and HBV-infected patients were immunostained to detect DDX6 and Dcp1 (core P-body components). Confluent microscopy revealed that HCV specifically inhibited P-body formation in human hepatocytes regardless of viral genotype, inflammation grade, or duration of infection (acute or chronic). This alteration was reversed after treatment-induced viral clearance. The study researchers describe finding an unexpected heterogeneity in P-body composition in vivo, which they suggest might reflect functional specialisations.

Comment: Processing (P)-bodies are microscopically distinct aggregates of proteins and ribonucleic acids (RNAs) that play a key role in cellular homeostasis by contributing to messenger RNA (mRNA) storage, mRNA degradation and microRNA-mediated suppression of mRNA translation. This is the first study to demonstrate that P-body composition and abundance in human hepatocytes are disturbed by HCV infection. P-body disturbance was found to occur independently of HCV genotype, degree of inflammation or duration of HCV infection. The findings extend those previously reported in human hepatoma cell lines. While the full implications of these observations remain to be elucidated, the demonstration of perturbation of P-bodies by HCV adds yet another level of mechanistic complexity to our current understanding of the pathophysiology of HCV infection at the molecular level.

Reference: J Hepatol. 2015;62(4):785-90

Abstract

MDA5 plays a critical role in interferon response during hepatitis C virus infection

Authors: Cao X et al.

Summary: This study was designed to identify the viral sensor that triggers interferon response in hepatocytes during HCV infection. By generating a hepatic cell line stably expressing mutant MAVS, the study researchers were able to show that HCV infection induced a robust interferon response regardless of viral genotype, degree of inflammation or duration of HCV infection. The findings extend those previously reported in human hepatoma cell lines. While the full implications of these observations remain to be elucidated, the demonstration of perturbation of P-bodies by HCV adds yet another level of mechanistic complexity to our current understanding of the pathophysiology of HCV infection at the molecular level.

Comment: This study extends current understanding of innate immune mechanisms relevant to HCV infection and, in particular, how host cells recognise HCV to initiate interferon signalling. While previous studies performed using an artificial RNA transfection model have suggested that HCV is sensed by the RIG-I as the pattern recognition receptor (PRR), the current study employed a novel HCV infectious cell culture model and found that interferon production in response to HCV infection is mainly dependent upon MDA5, rather than RIG-I, as the PRR. The exact nature of the HCV pathogen-associated molecular pattern recognised by MDA5 and leading to intracellular interferon production remains to be characterised. An interesting finding is that HCV infection does not immediately activate interferon signalling within infected cells, raising the possibility that recruitment of a currently undisclosed additional biological factor may be necessary to facilitate binding of HCV to MDA5.


Abstract

Treatment cessation of entecavir in Asian patients with hepatitis B e antigen negative chronic hepatitis B: a multicentre prospective study

Authors: Seto WK et al.

Summary: These researchers evaluated the effect of discontinuing entecavir therapy in 184 Asian patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B virus (HBV) infection treated for ≥2 years and who had undetectable HBV DNA levels on ≥3 separate occasions 6 months apart before treatment cessation. The study employed a novel HCV infectious cell culture model and found that interferon production in response to HCV infection is mainly dependent upon MDA5, rather than RIG-I, as the PRR. The exact nature of the HCV pathogen-associated molecular pattern recognised by MDA5 and leading to intracellular interferon production remains to be characterised. An interesting finding is that HCV infection does not immediately activate interferon signalling within infected cells, raising the possibility that recruitment of a currently undisclosed additional biological factor may be necessary to facilitate binding of HCV to MDA5.

Reference: Gut. 2015;64(4):667-72

Abstract

The combination of simeprevir and sofosbuvir is more effective than that of peginterferon, ribavirin, and sofosbuvir for patients with hepatitis C-related Child’s class A cirrhosis

Authors: Pearlman SL et al.

Summary: This study recruited 82 patients with chronic HCV genotype 1a infection and Child’s grade A cirrhosis. Fifty patients had not responded to treatment with peginterferon and ribavirin (null responders) and 32 were treatment-naïve; 48% were African American. Patients were randomly assigned to simeprevir (150 mg/day) and sofosbuvir (400 mg/day) (n=58 in the final analysis) or to peginterferon (150 mg/day) and sofosbuvir (400 mg/day) (n=24 in the final analysis), for 12 weeks. Overall, 93% of patients treated with simeprevir and sofosbuvir achieved SVR12 compared with 75% of patients on the interferon-containing regimen (p=0.02). In addition, the simeprevir/sofosbuvir regimen was associated with a lower rate of virological relapse (p=0.009), better self-reported outcomes and more adverse events, compared with the interferon-containing regimen.

Comment: This randomised study compared the safety and the efficacy of peginterferon/ribavirin/sofosbuvir (a nucleotide analogue inhibitor of HCV polymerase) to those of simeprevir (a second-wave, first-generation HCV protease inhibitor) and sofosbuvir, each for 12 weeks, in a difficult-to-treat population of patients with well-compensated HCV genotype 1a-induced cirrhosis, including both treatment-naïve subjects and prior null responders to peginterferon/ribavirin. Although including only relatively small numbers in the various treatment arms, the study found that, overall, the all-oral regimen of simeprevir and sofosbuvir was associated with not only improved tolerability with fewer adverse events but also a significantly higher SVR than peginterferon/ribavirin/sofosbuvir (93% versus 75%, respectively). Differences in SVR related to the two treatments did not reach statistical significance when treatment-naïve (95% versus 80%) and prior null responders (92% versus 64%) were considered separately. Assessment in larger cohorts of patients will clearly be important.

Reference: Gastroenterology. 2015;148(4):762-70

Abstract

Independent commentary by Professor Stephen Riordan.

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**Abstract**

**Reference:** Liver Int. 2015;35(4):1290-302

**Authors:** Hosaka T et al.

**Summary:** In this study, 202 Japanese patients with HBsAg-positive chronic HBV received lamivudine as first-line therapy. The study aimed to determine whether polymorphisms in the human leucocyte antigen (HLA)-DP genes are associated with decreases in HBsAg levels and seroclearance. All patients underwent HLA-DP genotyping (HLA-DPA1 rs3077 and HLA-DPB1 rs9277535) and were categorised into two groups: patients who achieved virological response without rescue therapy (cohort 1) and those who did so with rescue therapy (cohort 2). Between years 3 and 9, serum HBsAg levels declined significantly from baseline among patients in cohort 1 possessing ≥2 A-alleles at rs3077 and rs9277535; significantly more of these patients achieved decreases in HBsAg ≥0.5 log IU/mL compared with patients with <2 A-alleles (71.8% vs 38.9%; p=0.004). However, cumulative HBsAg seroclearance rates did not differ significantly between patients with ≥2 and those with <2 A-alleles in cohort 1. In cohort 2, HBsAg seroclearance rates were higher in patients with ≥2 A-alleles than in those with <2 A-alleles (p=0.003).

**Comment:** Genome-wide association studies have suggested that the human leucocyte antigen (HLA)-DP locus, located on chromosome 6, is associated with a likelihood of persistent HBV infection. Two single nucleotide polymorphisms (SNPs) in HLA-DPA1 and HLA-DPB1, namely HLA-DPA1 rs3077 and HLA-DPB1 rs9277535, are strongly associated with HBV persistence, while the minor alleles of both rs3077 and rs9277535 seem to be protective against chronic HBV infection. This study extends these observations by demonstrating that, in Japanese patients with HBsAg-positive chronic HBV infection treated with lamivudine with or without adefovir dipivoxil, the minor alleles at rs3077 and rs9277535 are associated with increased treatment-induced HBsAg reduction. No such association was demonstrated in HBeAg-negative patients receiving nucleos(t)ide analogue treatment. The results require confirmation in larger cohorts of patients in other geographical locations, as well as those treated with potent antiviral agents with high barriers to resistance, such as entecavir and tenofovir disoproxil fumarate.

**Reference:** Liver Int. 2015;35(4):1334-40

**Abstract**

**Reference:** Nephrology Research Review

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