This phase III study recruited 180 nucleos(t)ide-naïve children and adolescents (2–17 years incl.) with hepatitis B e antigen-positive chronic hepatitis B virus (HBV) infection and randomised them to blinded treatment with entecavir (n=120) or placebo (n=60) for a minimum of 48 weeks. After week 48, patients with HBeAg seroconversion continued blinded treatment; those without switched to open-label entecavir. After 48 weeks of treatment, rates for the primary endpoint (HBeAg seroconversion and HBV DNA <50 IU/mL at week 48) were significantly higher with entecavir than with placebo (24.2% vs 3.3%; p=0.0008). Entecavir was also associated with higher response rates versus placebo for the key week 48 secondary endpoints: HBV DNA <50 IU/mL (49.2% vs 3.3%; p<0.0001); alanine aminotransferase normalisation (67.5% vs 23.3%; p<0.0001); and HBeAg seroconversion (24.2% vs 10.0%; p=0.0210). All efficacy endpoints increased between weeks 48 and 96 in the entecavir cohort, including virological suppression, which was increased from 49% to 64%. The cumulative probability of emergent entecavir resistance through years 1 and 2 of entecavir was 0.6% and 2.6%, respectively. Entecavir was well tolerated. There were no between-group differences in adverse events or changes in growth.

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Welcome to issue 29 of Hepatitis Research Review.

Promising results from the TURQUOISE-III phase IIb, open-label study suggest that a treatment regimen of ombitasvir/paritaprevir/ritonavir administered with dasabuvir for 12 weeks is a highly efficacious treatment for HCV genotype 1b infection with compensated cirrhosis, even without ribavirin. All study participants achieved SVR (HCV RNA <25 IU/mL) at 12 weeks post-treatment. Treatment was well tolerated with a low rate of serious adverse events and none of the patients discontinued treatment prematurely.

A 12-week all-oral direct-acting antiviral (DAAs) regimen of ombitasvir plus dasabuvir has shown high rates of treatment response and good tolerability in a large US-based prospective observational cohort study of patients with HCV genotype 1 infection, giving confidence that currently approved DAAs will likely achieve good outcomes in ‘real world’ (non-clinical trial-based) settings.

A large, retrospective analysis of data from the Veteran Affairs Clinical Case Registry suggests that statin use among patients with HCV and compensated cirrhosis is associated with a more than 40% lower risk of cirrhosis decompensation and death. The study concludes that while statins cannot yet be recommended widely for these patients, their use should not be avoided.

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

Professor Stephen Riordan
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Randomized, controlled trial of entecavir versus placebo in children with hepatitis B envelope antigen-positive chronic hepatitis B

Authors: Jonas MM et al.

Summary: This phase III study recruited 180 nucleoside-naïve children and adolescents (2–17 years incl.) with hepatitis B envelope antigen (HBeAg)-positive chronic hepatitis B virus (HBV) infection and randomised them to blinded treatment with entecavir (n=120) or placebo (n=60) for a minimum of 48 weeks. After week 48, patients with HBeAg seroconversion continued blinded treatment; those without switched to open-label entecavir. After 48 weeks of treatment, rates for the primary endpoint (HBeAg seroconversion and HBV DNA <50 IU/mL at week 48) were significantly higher with entecavir than with placebo (24.2% vs 3.3%; p=0.0008). Entecavir was also associated with higher response rates versus placebo for the key week 48 secondary endpoints: HBV DNA <50 IU/mL (49.2% vs 3.3%; p<0.0001); alanine aminotransferase normalisation (67.5% vs 23.3%; p<0.0001); and HBeAg seroconversion (24.2% vs 10.0%; p=0.0210). All efficacy endpoints increased between weeks 48 and 96 in the entecavir cohort, including virological suppression, which was increased from 49% to 64%. The cumulative probability of emergent entecavir resistance through years 1 and 2 of entecavir was 0.6% and 2.6%, respectively. Entecavir was well tolerated. There were no between-group differences in adverse events or changes in growth.

Comment: Here, the authors report on a multicentre, placebo-controlled study on the use of entecavir for a minimum 48 weeks in 180 nucleoside-naïve children aged between 2 and 18 years with chronic, replicative, HBeAg+ve HBV infection. The rate of hepatitis B e antigen/hepatitis B e antibody seroconversion along with HBV DNA <50 IU/mL in children managed with entecavir was 24.2%, significantly higher than that in the placebo-treated group (3.3%). Pre-treatment HBV DNA levels <10^5 IU/mL and a non-D HBV genotype were each significantly associated with an increased likelihood of response to entecavir. Such an association with HBV genotype has not been reported in the adult population and remains to be confirmed in larger series. Similarly, an apparent rate of resistance in the order of 2.6% in the second year of treatment is substantially higher than that recorded in adults and is currently unexplained.


A CURE* FOR GT1† AND GT3 CHRONIC HCV HAS NOW BEEN GIVEN THE GREEN LIGHT1-4

*Sustained virological response (SVR) – undetectable HCV RNA 12 or 24 weeks post-treatment end – corresponds to a definitive cure in >99% of cases of hepatitis C.

Abstract

A large, retrospective analysis of data from the Veteran Affairs Clinical Case Registry suggests that statin use among patients with HCV and compensated cirrhosis is associated with a more than 40% lower risk of cirrhosis decompensation and death. The study concludes that while statins cannot yet be recommended widely for these patients, their use should not be avoided.

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Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct-acting antiviral agents

Authors: Sise ME et al.

Summary: These researchers retrospectively analysed outcomes of 12 patients (median age 61 years) with hepatitis C virus (HCV)-associated mixed cryoglobulinemia syndrome (MCS) given all-oral direct-acting antiviral (DAA) therapy with sofosbuvir-based regimens in a healthcare network; 6 patients had cirrhosis and 7 had renal involvement (as determined by kidney biopsy [n=5] or by ≥2 of the following clinical findings: reduced kidney function, proteinuria, or haematuria with other causes excluded [n=2]). Median baseline serum creatinine was 0.97 mg/dL. HCV-MCS was defined by circulating cryoglobulin associated with systemic vasculitis symptoms. A cohort of patients treated with pegylated interferon and ribavirin served as historical controls. Sustained virological response rates at 12 weeks (SVR12) for the DAA regimens were 83% versus just 10% for historical controls treated with pegylated interferon and ribavirin. Patients with glomerulonephritis who achieved SVR12 experienced an improvement in serum creatinine and a reduction in proteinuria. Cryoglobulin levels decreased in 89% of patients, with median percent decreasing from 1.5% to 0.5% and completely disappearing in 4 of 9 cases who had post-treatment cryoglobulin measurements. Serious adverse events were infrequent (17%), whereas all of the historical controls experienced at least one adverse event and 50% discontinued treatment early due to adverse events.

Comment: MCS is due to HCV infection in up to 90% of cases. This retrospective case series reports on the efficacy and safety of interferon-free, sofosbuvir-based (with simeprevir, n=8 or ribavirin, n=4) therapy, mostly for 12 weeks, in 12 patients with HCV-related MCS. SVR12 was 83% and was associated with improvement in renal function and proteinuria in those with glomerulonephritis. Treatment was generally well tolerated. The results are superior to those achieved using historical interferon and ribavirin-based therapy for HCV-related MCS and suggest that direct-acting antiviral (DAA) therapy should be considered as first-line treatment for this disorder.


Abstract

DEPDC5 variants increase fibrosis progression in Europeans with chronic hepatitis C virus infection

Authors: Burza MA et al.

Summary: This study examined the effect of genetic variants DEPDC5 rs1012068 and MICA rs2596542 on hepatocellular carcinoma (HCC) onset in Europeans with chronic HCV infection. Data were analysed from a Northern Italian discovery cohort (n=477) and independent validation cohorts, consisting of a cross-sectional German cohort (n=415) and a prospective cohort (n=247). All cohorts consisted of therapy-naïve patients with chronic HCV infection and no HBV or HIV co-infection. In the discovery cohort, DEPDC5 rs1012068 and MICA rs2596542 were not associated with HCC (n=150), although there was a higher prevalence of DEPDC5 rs1012068 in the 930 patients with cirrhosis than in those with no/mild cirrhosis (p=0.049); this association was confirmed in the cross-sectional validation cohort (p=0.006). Furthermore, DEPDC5 rs1012068 was associated with a higher fibrosis progression rate in the prospective cohort (p=0.027). An analysis of the distribution of DEPDC5 non synonymous variants in the overall cross-sectional cohort (n=912) revealed that carriage of at least one variant was associated with a 54% increase in the risk of moderate/severe fibrosis (p=0.040). The researchers then identified high DEPDC5 expression in immortalised LX-2 human hepatic stellate cells. Down-regulation of DEPDC5 was found to increase B-catenin expression and matrix metalloproteinase 2 (MMP2) production in these cells.

Comment: Two previous genome-wide association studies have suggested that non-coding variants in the DEP domain-containing 5 (DEPDC5) and in the MHC class I polypeptide-related sequence A (MICA) loci, namely DEPDC5 rs1012068 and MICA rs2596542, respectively, confer susceptibility to complicating HCC in Asian patients with chronic HCV infection. This analysis was performed to investigate for any effect of these genetic variants on hepatic fibrosis and HCC development in HCV patients of European ancestry. The findings suggest that DEPDC5 rs1012068, but not MICA rs2596542, promotes severe hepatic fibrosis in such patients, with in vitro studies using an immortalised human stellate cell line pointing to this effect being due to an interaction between the DEPDC5 variant and the B-catenin pathway, leading to increased synthesis of MMP2. By contrast, neither DEPDC5 rs1012068 nor MICA rs2596542 was associated with HCC development in HCV patients of European descent.


Abstract
Cost-effectiveness of new antiviral regimens for treatment-naive U.S. veterans with hepatitis C
Authors: Chidi AP et al.
Summary: A Markov model was developed to compare the cost-effectiveness of sofosbuvir/ledipasvir or ombitasvir/ritonavir/paritaprevir/dasabuvir in 3 scenarios involving 60-year-old US veterans with untreated genotype 1 HCV seeking treatment: (1) any patient seeking treatment; (2) only patients with advanced fibrosis or cirrhosis; or (3) patients with advanced disease first and healthier patients 1 year later. Treating any patient with ombitasvir-based therapy was the preferred strategy ($US35,560; 14.0 quality-adjusted life years [QALYs]). All other strategies yielded greater costs/QALY gained.


Hepatitis B virus-human chimeric transcript HBx-LINE1 promotes hepatic injury via sequestering cellular microRNA-122
Authors: Liang HW et al.
Summary: This investigation describes an inverse correlation between HBx-LINE1 (a hybrid RNA transcript of the human LINE1 and the HBV-encoded X gene generated in tumour cells of HBV-positive HCC) and the liver-specific microRNA (miR-122) in HBV-positive HCC tissue specimens. Mice administered HBx-LINE1 developed abnormal mitotic processes in liver cells in HBV-positive HCC tissue specimens. Mice administered HBx-LINE1 developed abnormal mitotic processes in liver cells and hepatic injury; these effects were completely abolished by miR-122.

Comment: MicroRNAs (miRNAs) are small, non-coding RNAs that post-transcriptionally regulate gene expression by repressing specific messenger RNA targets. miR-122, the predominant miRNA in the liver with potent anti-inflammatory and tumour suppressor effects, is an essential host factor for HCV genome stability but inhibits replication of HBV. Mechanisms by which HBV may escape the effects of this antiviral miRNA in those with chronic infection have remained unknown. Thus, this study, demonstrating that a hybrid HBV-human transcript commonly found in HBV-associated HCC serves to sequester miR-122, is important in providing a molecular mechanism by which HBV may inhibit miR-122 activity, thereby favouring HBV replication and promoting HCC progression. The findings raise the potential for new antiviral strategies aimed at restoring intra-hepatic miR-122 activity in patients with chronic HBV infection, especially in the setting of complicating HCC.

Reference: J Hepatol. 2016;64(2):278-91

Daclatasvir plus simeprevir with or without ribavirin for the treatment of chronic hepatitis C virus genotype 1 infection
Authors: Zeuzem S et al.
Summary/Comment: This randomised, open-label phase II study evaluated the efficacy of daclatasvir, an NS5A inhibitor, in combination with simeprevir, an NS3/4A inhibitor, with or without ribavirin, for up to 24 weeks in 168 patients with chronic genotype 1 HCV infection (mostly genotype 1b; 35% with compensated cirrhosis), including both treatment-naïve and previous null responders to pegylated interferon and ribavirin therapy. SVR12 in treatment-naïve and previous null responder genotype 1b patients was 84.9% and 69.6%, respectively, including 72.4% and 82.2% in those with and without cirrhosis. The addition of ribavirin apparently had an inconsistent effect on SVR12. Overall SVR12 was 66.7% in genotype 1a patients. These efficacies in genotype 1b and 1a patients are less than that recorded with other direct-acting antiviral (DAA) regimes, which should be viewed as preferred options.

Reference: J Hepatol. 2016;64(2):292-300

Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12 weeks
Authors: Feld JJ et al.
Summary: The TURQUOISE-III phase IIIb study investigated the safety and efficacy of ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) and dasabuvir (DSV) without ribavirin, for 12 weeks in treatment-naïve and peginterferon/ribavirin treatment-experienced adults with chronic HCV genotype 1b infection and compensated cirrhosis. Co-formulated OBV/PTV/r was administered once daily (25/150/100 mg) and DSV 250 mg twice daily. At baseline, the majority of patients had prior treatment experience with pegylated interferon/ribavirin (55%) and had the IL28B non-CC genotype (83%); 22% had platelet counts <90×10^9/L, and 17% had albumin <3.5 g/dL. All 60 study participants completed treatment and all achieved SVR12. The most common adverse events were fatigue (22%), diarrhoea (20%), and headache (18%). Only one patient (1.7%) experienced a serious adverse event. Laboratory abnormalities were uncommon and not clinically significant.

Comment: This phase IIIb, open-label study assessed safety and efficacy of a 12-week course of ombitasvir, an NS5A inhibitor co-formulated with ritonavir-enhanced paritaprevir, an NS3/4A inhibitor, along with dasabuvir, an NS5B inhibitor, in 60 adults with compensated cirrhosis due to chronic genotype 1b HCV infection, including both treatment-naïve and previous failed pegylated interferon and ribavirin treatment groups. SVR12 was 100%. Treatment was well tolerated, with, in particular, lower rates of anaemia than documented in a previous study in which ribavirin use was incorporated. The results indicate that this direct-acting antiviral (DAA) regimen is highly efficacious in patients with genotype1b-related compensated cirrhosis, even without ribavirin, which is better avoided to limit the likelihood of side effects.

Reference: J Hepatol. 2016;64(2):301-7

Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving daclatasvir and simeprevir with or without ribavirin
Authors: Park YK et al.
Summary/Comment: Animal model and cell culture studies have clearly demonstrated that tumour necrosis factor-alpha (TNF-α) inhibits HBV replication via nuclear factor kappa B (NF-κB) signalling, although responsible downstream molecular mechanisms have remained relatively unknown. Recent data suggest that p22-FLIP, a cleavage product of the cellular FLICE-inhibitory protein (c-FLIP), can induce NF-κB signalling in lymphocytes. On that background, this study, performed using both a hepatoma cell line and primary human hepatocytes, investigated whether p22-FLIP may be involved in NF-κB/NF-κB-mediated suppression of HBV replication. The findings are important in demonstrating that p22-FLIP cleavage from c-FLIP is generated via the TNF-α/NF-κB pathway and, in turn, inhibits HBV transcription and replication through both the upregulation of hepatocyte nuclear receptor 3β and the downregulation of hepatocyte nuclear factor 4a, documenting a novel mechanism by which TNF-α non-cytolytically suppresses HBV during its natural history.

Reference: J Hepatol. 2016;64(2):268-77

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Effectiveness of simeprevir plus sofosbuvir, with or without ribavirin, in real-world patients with HCV genotype 1 infection

Authors: Sukowski MS et al.

Summary: This investigation assessed demographic, clinical, and virological data, as well as reports of adverse outcomes, from HCV-TARGET, a prospective observational cohort study of patients undergoing HCV treatment in routine clinical care settings. From January through October 2014, 836 patients with HCV genotype 1 infection began 12 weeks of treatment with simeprevir plus sofosbuvir (treatment duration of up to 16 weeks); ribavirin was also administered to 169 patients. The majority of patients were male (61%), 76% were Caucasian, 13% were black (13%), and 59% had cirrhosis. Most patients had failed prior treatment with peginterferon and ribavirin without (46%) or with telaprevir or boceprevir (12%). The overall SVR rate was 84% (675 of 802 patients). In model-adjusted estimates, patients with cirrhosis, prior decompensation, and previous protease inhibitor treatments were less likely to achieve an SVR. The addition of ribavirin had no detectable effects on SVR. The most common adverse events were fatigue, headache, nausea, rash, and insomnia. Serious adverse events and treatment discontinuation occurred in only 5% and 3% of participants, respectively.

Comment: Concern exists that the translation of new direct-acting antiviral (DAA) treatments for HCV infection from the clinical trial setting to clinical practice may be associated with both reduced rates of SVR and increased rates of adverse events. This large observational cohort study assessed the efficacy and safety of combination sofosbuvir (an NS5B inhibitor) and simeprevir (an NS3 inhibitor), mostly without ribavirin, for 12 weeks in 836 genotype 1 HCV patients managed in routine clinical practice at 54 centres in the United States, including 58.7% with cirrhosis and 61% with non-response to prior treatments. SVR12 was 84% overall and 81% in patients with cirrhosis, with only 2% of patients discontinuing therapy because of adverse events. The findings give confidence that similar efficacies and safety data related to DAA therapy to those attained in clinical trials are likely to be achieved in clinical practice.

Reference: Gastroenterology. 2016;150(2):419-29

Statins are associated with a decreased risk of decompensation and death in veterans with hepatitis C-related compensated cirrhosis

Authors: Mohanty A et al.

Summary: This retrospective analysis of records from the Veteran Affairs Clinical Case Registry identified 40,512 patients with HCV-related compensated cirrhosis in the period from January 1996 through December 2009; 2802 of the cohort filled prescriptions for statins. A propensity score model was developed, using variables associated with statin prescription, in which 685 statin users were matched with 2062 nonusers. Discrimination of the propensity score model was 0.92. Statin users had a lower risk of decompensation (HR 0.55; 95% CI, 0.39 to 0.77) and death (HR 0.56; 95% CI, 0.46 to 0.69), compared with nonusers. Findings persisted after adjustment for age, FIB-4 index score, serum level of albumin, model for end-stage liver disease and Child-Turcotte-Pugh scores (HR for decompensation, 0.55; 95% CI, 0.39 to 0.78), and death (HR 0.55; 95% CI, 0.45 to 0.68).

Comment: This large, retrospective propensity score-matched study, performed in patients with compensated cirrhosis due to HCV infection, documents a 40%-lower risk of decompensation and death in patients receiving statin therapy. In particular, rates of development of ascites, variceal haemorrhage and hepatocellular carcinoma were each apparently significantly reduced with statin use. The findings suggest, at the very least, that, even though statins can be hepatotoxic, their use should not be avoided in HCV patients with compensated cirrhosis and provide justification for a future large-scale, prospective, placebo-controlled, randomised trial in those with compensated cirrhosis due to a range of aetiologies.