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Welcome to issue 35 of Hepatitis Research Review.

Interesting findings are reported in this issue from investigations describing possible novel mechanisms for HCV escape from natural killer cell-mediated attack and a novel predictive marker that may predict response to pegylated-interferon-based therapy in hepatitis B e antigen-positive chronic HBV infection.

Data from the phase III OPTIMIST-1 and OPTIMIST-2 trials are discussed in this issue and demonstrate good efficacy and tolerability of the all-oral regimen of simeprevir plus sofosbuvir in genotype 1 HCV infection, including treatment-naïve and treatment-experienced patients, with or without cirrhosis.

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

Professor Stephen Riordan
stephen.riordan@researchreview.com.au

The applicability of hepatocellular carcinoma risk prediction scores in a North American patient population with chronic hepatitis B infection

Authors: Abu-Amara M et al.

Summary: Several scoring systems have been developed that successfully predict the risk of hepatocellular carcinoma (HCC) in Asian patients with chronic hepatitis B (CHB) infection. These researchers examined the predictability of five HCC risk prediction models (CU-HCC, REACH-B, NGM1-HCC, NGM2-HCC and GAG-HCC) in a heterogeneous cohort of 2105 North American patients with CHB. Seventy patients developed HCC. In all models, increasing risk score was associated with HCC. The CU-HCC model had the highest predictive ability, as assessed by the area under the receiver operating characteristic curve (AUROC; 0.85 in Asian and 0.91 in non-Asian patients). In all models, patients identified as low risk had a very low incidence of HCC (0–0.15 per year); the CU-HCC and GAG-HCC models identified the highest proportions of patients identified as low risk (67% and 78%, respectively). The risk of HCC was similar to predicted for low-risk and medium-risk patients but was lower than predicted for high-risk patients. Treated patients had a lower than predicted risk of HCC, particularly in non-cirrhotic high-risk patients with longer follow-up.

Comment: Five scoring systems to predict risk of HCC complicating chronic HBV infection have been developed and validated in Asian populations. The aim of this current study was to assess the accuracy of these scoring systems in a heterogeneous, North American population of mixed viral genotypes and ethnicities, representing the largest cohort of patients with chronic HBV infection and complicating HCC assessed to date. Each of the scoring systems was found to perform well, especially those systems taking into account liver function as well as viral activity, and especially in patients with low risk scores. Lower observed than predicted risk for HCC occurred in patients stratified to medium- and high-risk groups, with this discrepancy apparently due at least in part to antiviral treatment. A pragmatic message from the study is that HCC risk is truly low in those with low risk scores, irrespective of the scoring system used, such that less intensive surveillance may be reasonable in this group.


Abstract

Abbreviations used in this issue:

- CHB = chronic hepatitis B
- GT = genotype
- HBeAg = hepatitis B e antigen
- HBsAg = hepatitis B surface antigen
- HCV = hepatitis C virus
- HEV = hepatitis E virus
- NK = natural killer
- OR = odds ratio
- SVR = sustained virological response

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Factors associated with spontaneous clearance of chronic hepatitis C virus infection

Authors: Bulleen N et al.

Summary: These researchers retrospectively analysed data from a cohort of Scottish patients who underwent HCV testing between 1994 and 2013. Cases (n=50) were defined as untreated patients who spontaneously resolved chronic HCV infection, with ≥2 sequential samples positive for HCV RNA ≥6 months apart followed by ≥1 negative test. Controls (n=200) were those who remained chronically infected, with ≥2 positive samples ≥6 months apart with no subsequent negative samples. The incidence rate of spontaneous clearance was 0.36/100 person-years of follow-up, occurring after a median 50 months’ infection. Spontaneous clearance was positively associated with female gender, patients infected at a younger age, those with lower levels of HCV in the blood, or who were co-infected with HBV infection. It was negatively associated with current intravenous drug use.

Comment: Spontaneous clearance of acute HCV infection occurs within 6 months in 20% to 40% of cases, with a favourable interleukin-28B (IL28B) gene polymorphism the strongest predictor of this outcome. Factors associated with spontaneous clearance of HCV once in the chronic phase of infection are less well understood. This retrospective, case-control analysis performed in Scotland, constituting the largest cohort of patients with evidence of spontaneous clearance of chronic HCV infection studied to date, addressed this issue. Spontaneous clearance of chronic HCV infection was found to be rare, with an incidence of 0.19–0.36 per 100 person-years. Female gender, younger age at infection, a low HCV viral load and co-infection with HBV were found to be associated with an increased likelihood of spontaneous chronic HCV clearance. A cohort of patients who spontaneously cleared chronic HCV in the setting of an episode of hepatic functional decompensation was identified, suggesting that reassessment of HCV status may be warranted following such an episode.

Reference: J Hepatol. 2016;65(2):266-72

Sequence variations in HCV core-derived epitopes alter binding of KIR2DL3 to HLA-C*03:04 and modulate NK cell function

Authors: Lunemann S et al.

Summary: For this investigation, 200 overlapping peptides, covering the non-structural protein 3 (NS3) and core protein of HCV genotype 1, were screened by transporter for antigen presentation-deficient 722.221 cells stably transduced with human leukocyte antigen (HLA)-C*03:04. The aim was to assess the effects of these viral peptides on HLA stabilisation, changes in killer cell immunoglobulin-like receptor (KIR) binding and primary NK cell function.

Comment: NK cells are an important component of the innate immune system that can respond rapidly to encountered pathogens without the requirement for prior sensitisation. Important among NK receptors are the killer cell immunoglobulin-like receptors (KIRs), which interact with HLA class I molecules on the surfaces of other cells. This is the first study to investigate the possible role of HCV peptides presented by HLA class I molecules in KIR binding and, hence, KIR/NK cell function. The findings are important in demonstrating that the HLA-C*03:04-restricted peptide, YIPLVGAPL, derived from the core protein of HCV genotype 1, binds to the inhibitory NK cell receptor, KIR2DL3, and thereby inhibits KIR2DL3/NK cell function, providing a possible novel mechanism for HCV escape from NK cell-mediated attack.

Reference: J Hepatol. 2016;65(2):252-8

HLA-C and KIR combined genotype as new response marker for HBeAg-positive chronic hepatitis B patients treated with interferon-based combination therapy

Authors: Steima F et al.

Summary: This study involved 86 patients with chronic HBV infection (41 were positive for hepatitis B e antigen [HBeAg], 45 were HBeAg-negative) who were treated with combination pegylated interferon alfa-2a and adefovir for 48 weeks and followed up until week 72. Genotyping of 12 single nucleotide polymorphisms (SNPs) in or near the HLA-C gene revealed that only one (the rs2308557 SNP) was significantly associated with response in HBeAg-positive CHB patients (p=0.003). This SNP is linked to the HLA-C group C1 or C2 classification, which controls KIR binding. In the HBeAg-positive cohort, the combination of KIR2DL1 with its ligand HLA-C2 was observed significantly more often in patients classified as responders compared with the non-responders (13/14 vs 11/27, respectively; p=0.001). Patients with the KIR2DL1/C2 genotype had significantly higher baseline ALT levels (136 vs 50 U/L; p=0.002) than patients without this combination. Furthermore, KIR2DL1-C2 predicted response independently of HBV genotype and ALT at baseline.

Comment: Further to the analysis of the possible importance of HLA-C and KIRs on NK cells with regard to HCV clearance discussed in the previous study, this study was performed to assess whether HLA-C and KIR genotypes may be associated with response to combination pegylated-interferon (PEG-IFN) and adefovir antiviral treatment in patients with chronic HBV infection. In HBeAg+ patients, the authors found that a favourable KIR2DL1 genotype in combination with an HLA-C2 allele was associated with treatment response (HBV DNA <2,000 IU/mL, HBeAg loss and normalisation of alanine aminotransferase [ALT] level), irrespective of HBV genotype or baseline ALT level, being present in 93% of responders and 41% of non-responders. The findings suggest that this particular HLA-C/KIR combination may represent a novel predictive marker for response to PEG-IFN-based therapy in patients with HBeAg+ chronic HBV infection.

Reference: J Viral Hepat. 2016;23(8):652-9
Hepatitis B e antigen and its precursors promote the progress of hepatocellular carcinoma by interacting with NUMB and decreasing p53 activity
Authors: Liu D et al.

Summary/Comment: It has been proposed that HBeAg may contribute to the risk of HCC in patients with chronic HBV infection. It was recently shown that the precore G1896A mutant is associated with a reduced risk of HCC, suggesting that HBeAg/precore may contribute to hepatocarcinogenesis. However, a precise pathogenic role is yet to be elucidated. This study addressed this issue. The authors demonstrate that HBeAg/precore can disrupt the tricomplex comprised of (i) the p53 tumour suppressor protein; (ii) the E3 ubiquitin ligase, HDM2 and (iii) NUMB, a cell fate determinant that antagonises the activity of the plasma receptor of the NOTCH family. This disruption results in decreased stability of the p53 protein and increased growth of hepatoma cells. The findings represent the discovery of another novel molecular mechanism by which HBV mitigates the stability of p53 and predisposes to HCC.
Simeprevir plus sofosbuvir (12 and 8 weeks) in hepatitis C virus genotype 1-infected patients without cirrhosis: OPTIMIST-1, a phase 3, randomized study

Authors: Kwo P et al.

Summary: OPTIMIST-1 randomised 310 non-cirrhotic, treatment-naive and treatment-experienced patients with genotype 1 HCV infection to open-label, once-daily treatment with simeprevir 150 mg plus sofosbuvir 400 mg for 12 weeks (n=155) or 8 weeks (n=155). The primary efficacy endpoint was SVR rate 12 weeks after end of treatment (SVR12). Superiority in SVR12 was assessed for simeprevir+sofosbuvir at 12 and 8 weeks versus a composite historical control SVR rate. SVR12 with simeprevir+sofosbuvir for 12 weeks was superior to the historical control (97% vs 87%), whereas SVR12 with simeprevir+sofosbuvir for 8 weeks was not (83% vs 83%).

Comment: This open-label, phase 3 study addressed the efficacy of simeprevir and sofosbuvir in 310 non-cirrhotic, treatment-naive or-experienced, genotype 1 HCV patients, randomised to receive either 8 or 12 weeks of treatment. Overall SVR12 for 12 weeks of treatment was 97%, while that of 8 weeks of treatment was 83%, lower than an historical rate of 94% associated with ledipasvir/sofosbuvir therapy. Treatment was well tolerated. Of note, the presence of the Q80K polymorphism in genotype 1a HCV, a resistance-associated mutation that can decrease the efficacy of simeprevir, was associated with poor response to 8 weeks of treatment but did not significantly impact upon the results of 12 weeks of treatment. As expected, the presence of non-structural 5A polymorphisms did not influence the efficacy of simeprevir/sofosbuvir therapy and such treatment may be a particularly useful choice for those patients who harbour such mutations.


Abstract

Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: A phase 3 study (OPTIMIST-2)

Authors: Lawitz E et al.

Summary: In OPTIMIST-2, patients aged 18–70 years with chronic genotype 1 HCV infection and cirrhosis (METAVIR score F4) received once-daily oral simeprevir 150 mg plus sofosbuvir 400 mg for 12 weeks. The overall SVR12 rate of 83% met the primary objective of superiority versus a composite historical control (70%), SVR12 rates for treatment-naive and treatment-experienced patients were 88% and 79%, respectively. Adverse events occurred in 70% of patients; the majority of events (64%) were grade 1 or 2. Serious adverse events (none considered related to study treatment) occurred in 5% of patients, and 5% of patients discontinued study treatment due to adverse events.

Comment: This second study to be reported from the OPTIMIST program is also an open-label, phase 3 analysis of simeprevir and sofosbuvir for genotype 1 HCV, with 12 weeks of treatment this time focussed on treatment-naive or -experienced patients with well-compensated cirrhosis. As in non-cirrhotic patients, treatment was well-tolerated. Overall SVR was 83%, including 92% in those without the Q80K variant. However, outcomes were disappointing in patients with baseline serum albumin levels <40 g/L, in whom SVR12 was only 74%, and in genotype 1a patients with baseline Q80K, in whom SVR12 was also only 74%, such that simeprevir/sofosbuvir may not be the treatment of choice for these subgroups of genotype 1-infected cirrhotic patients.


Abstract

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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.

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100% cure rate in GT1b non-cirrhotic patients (n=301/301)^2

100% cure rate in GT1b treatment-naive patients, including compensated cirrhotics (n=232/232)^2

97% cure rate across GT1 (n=1062/1096)^2

*In a pooled analysis of patients receiving the recommended VIEKIRA PAK + R8V closing regimen: cure defined as <25 IU/mL HCV RNA 12 weeks post end-of-treatment (SVR12).

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