Welcome to issue 31 of Hepatitis Research Review.

European researchers report study results that look promising for a potential prophylactic vaccine. Their paper describes how a broadly reactive monoclonal antibody, AP33, efficiently protected humanised mice from a patient-derived HCV challenge. Furthermore, the researchers suggest that mAb AP33 may help to prevent HCV recurrence, as it had the ability to neutralise viral variants that escaped the humoral immune response and reinfected the liver graft of transplant patients.

Another study suggests that patients with HCV-associated advanced cirrhosis being treated with ribavirin therapy may be at increased risk for developing lactic acidosis. The study researchers recommend that ribavirin is used with caution in patients with decompensated liver disease.

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

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

Prolonged suppression of HBV in mice by a novel antibody that targets a unique epitope on hepatitis B surface antigen

Authors: Zhang TY et al.

Summary: These researchers tested the therapeutic effects of 11 monoclonal antibodies (mAbs) against various epitopes on viral surface protein in murine models of chronic HBV infection. The tests revealed that a novel class of mAbs, targeting a conserved GPCK(R)TCT epitope on hepatitis B surface antigen (HBsAg) profoundly suppressed HBsAg levels and HBV DNA for several weeks, following single-dose administration. Moreover, this novel mAb regimen prevented initial HBV infection and reduced viral dissemination from infected hepatocytes in human-liver-chimeric mice, and facilitated the restoration of anti-HBV T cell response in hydrodynamic injection-based HBV carrier mice.

Comment: Clearance of HBsAg is rarely achieved with currently available nucleos(t)ide analogues or interferon. mAb therapy directed against HBsAg offers the potential to reduce circulating HBsAg levels and thereby restore anti-HBV T cell responses otherwise exhausted by chronic HBV infection. This study identifies EGFP6-like mAbs, recognising a conserved epitope on HBsAg, as possessing more marked HBV suppressive effects than mAbs binding to other epitopes, resulting in reduction in both HBsAg and HBV DNA levels, along with augmented T cell-mediated immunity in a carrier mouse model. The findings indicate that Fcy-mediated phagocytosis is largely responsible for EGFP-6-induced suppression of viraemia and suggest that a humanised form should be explored for possible clinical application as a means of facilitating HBsAg clearance in patients with chronic HBV infection.


PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy

Authors: Papatheodoridis G et al.

Summary: Risk scores for HBV-related hepatocellular carcinoma (HCC) perform well in Asians but offer poor-moderate predictability in Caucasian patients with chronic HBV infection. This paper describes the development and validation of an accurate HCC risk score in 1815 adult Caucasians with chronic HBV and no HCC at baseline. The study participants were recruited from 9 centres. Treatment consisted of oral antiviral therapy with entecavir or tenofovir disoproxil fumarate for ≥12 months. Data from 8 centres formed the derivation dataset (n=1325) and a HCC risk score was developed based on multivariable Cox models and points system for the derivation dataset (n=1325) and a HCC risk score was developed based on multivariable Cox models and points system for simplification. Harrell’s c-index was used as discrimination, bootstrap for internal validation and the data from the 9th and largest centre validation dataset, (n=490) served as external validation. The 5-year cumulative HCC incidence rates were 5.7% and 8.4% in the derivation and validation datasets, respectively. In the derivation dataset, age, gender, platelets and cirrhosis were independently associated with HCC. The PAGE-B score was developed based on age, gender and platelets (c-index=0.82, 0.81 after bootstrap validation). The addition of cirrhosis did not substantially improve the discrimination (c-index=0.84). The predictability of PAGE-B score was similar (c-index=0.62) in the validation dataset. PAGE-B scores of c9, 10–17, ≥18 were associated with 5-year cumulative HCC incidence rates of 0%, 3%, 17%, respectively, in the derivation dataset and 0%, 4%, 16%, respectively, in the validation dataset.

Comment: The development of HCC remains a major complication in patients with chronic HBV infection, even in those managed with antiviral therapy. HCC risk scores applicable to untreated Asian patients are unsatisfactory for use in Caucasians. This large, multicentre cohort study is the first to evaluate an HCC risk score in Caucasian patients with chronic HBV infection managed for 5 years with entecavir or tenofovir disoproxil fumarate. Based on both derivation and validation cohorts and an optimism cut-off value, the findings indicate that a non-elevated PAGE-B score at baseline, based on patient age, gender and platelet count, carries a negative predictive value of 100% for HCC development during the first 5 years of antiviral therapy. Around one in ten Caucasian, chronic HBV patients who have an elevated PAGE-B score at baseline will develop HCC during this time and should be more closely monitored.

Reference: J Hepatol. 2016;64(4):800-6

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Abbreviations used in this issue:

AGD = antihepatitis B globulin; CHB = chronic hepatitis B virus; GT1 = genotype 1; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HEV = hepatitis E virus; IFN = interferon; PAGE-B = predictive model for anti-HBV therapy efficiency; PWID = people who inject drugs; STAT4 = signal transducer and activator of transcription 4; ASO = antisense oligonucleotide; WB = western blot.
**Lactic acidosis in patients with hepatitis C virus cirrhosis and combined ribavirin/sofosbuvir treatment**

**Authors:** Welker MW et al.

**Summary:** Outcomes are reported for 35 patients with HCV-associated advanced cirrhosis treated with sofosbuvir-based antiviral therapy with and without ribavirin. Adverse events including lactic acidosis (pH <7.35, lactate >20 mg/dL) were recorded 24 weeks before commencing study treatment and during (mean 18 weeks) antiviral therapy. Severe adverse events were observed in 15 (43%) patients before (24 weeks) and in 12 (34%) patients during antiviral therapy, the majority in association with acute-on-chronic hepatic decompensation. Five (14%) patients developed lactic acidosis during therapy; no such event was observed prior to therapy. Lactic acidosis was associated with hepatic decompensation including renal failure and infection, and was severe (pH <7.3) in 2 patients.

**Comment:** Current experience suggests sustained virological response rates with direct-acting antiviral therapies (DAAs) in patients with decompensated cirrhosis due to chronic HCV infection of around 85% to 90%, although safety and tolerance issues are particularly important in this group. This retrospective analysis adds to existing literature by demonstrating severe adverse events in nearly 35% of patients managed with various sofosbuvir-based regimens (with pegylated interferon and ribavirin; with ribavirin; with simeprevir ± ribavirin; with daclatasvir ± ribavirin), mostly due to acute-on-chronic hepatic decompensation and including lactic acidosis in 14%. The exact mechanism(s) remain(s) to be determined but, whatever the cause, the findings highlight the need for careful monitoring of patients with HCV-related cirrhosis managed with DAAs, especially those with decompensated hepatic function at baseline.

**Reference:** J Hepatol. 2016;64(4):290-9

**Abstract**

**In vivo reduction of hepatitis B virus antigenemia and viremia by antisense oligonucleotides**

**Authors:** Billioud G et al.

**Summary:** These researchers evaluated the efficacy of antisense oligonucleotide (ASO) technology in the inhibition of HBsAg production and viremia in HBV transgenic and hydrodynamic transfection murine models and in a cell culture HBV infection model. ASO treatment decreased serum HBsAg levels ≥2 logs in a dose and time-dependent manner; HBsAg decreased 2 logs in a week and was restored to baseline levels 4 weeks after a single ASO injection. ASO treatment effectively reduced HBsAg in combination with entecavir, whereas entecavir alone had no such effect. ASO treatment showed pan-genotypic antiviral activity in the hydrodynamic transfection system. cccDNA-driven HBV gene expression proved to be ASO-sensitive in HBV-infected cells in vitro.

**Comment:** High circulating levels of both HBsAg and hepatitis B e antigen promote HBV-specific T cell anergy in patients with chronic HBV infection. ASOs are small, single-stranded, target-specific nucleic acids that bind to complementary RNAs, leading to their degradation. Post-transcriptional gene silencing by means of ASO technology offers the possibility to reduce HBV gene expression and circulating HBV antigens. This is the first demonstration that a second-generation ASO, containing 2′-O-methoxyethyl sugar modifications that promote stability, can decrease HBV gene expression, replication, viremia and antigenaemia in a transgenic murine model. ASO therapy warrants further exploration for possible clinical application as a novel therapy for chronic HBV infection.

**Reference:** J Hepatol. 2016;64(4):781-9

**Abstract**

**Evaluation of APRI and FIB-4 scoring systems for non-invasive assessment of hepatic fibrosis in chronic hepatitis B patients**

**Authors:** WR Kim et al.

**Summary:** This paper reports on the performance of 2 non-invasive scoring systems, APRI (aspartate aminotransferase-to-platelet ratio index) and FIB-4 (fibrosis index based on 4 factors), in the prediction of fibrosis stage in chronic HBV. The study analysed demographic, histological and clinical laboratory data from 2 trials investigating tenofovir disoproxil fumarate in chronic HBV. Predicted fibrosis stage, based on established scales and cut-off values for APRI and FIB-4 scores, was compared with Ishak scores obtained from liver biopsy at baseline and at 240 weeks of follow-up. Baseline liver biopsy results obtained from 575 patients revealed that APRI and FIB-4 scores correlated with Ishak stage (p<0.01), but extensive overlap in the distribution of both scores across Ishak stages prevented accurate determination of fibrosis. The scores failed to detect the majority (81–89%) of patients with advanced fibrosis or cirrhosis. Similarly, 71% patients without fibrosis were misclassified as having clinically significant fibrosis. APRI and FIB-4 scores at week 240 tended to be low and underestimated fibrosis stage in the patients with liver biopsies after 240 weeks of therapy. Reductions in APRI or FIB-4 scores did not correlate with fibrosis regression after 240 weeks of antiviral therapy.

**Comment:** This study, performed in a large and well-characterised cohort of CHB patients enrolled in clinical trials, investigated whether two commonly used scoring systems for hepatic fibrosis complicating chronic HCV infection (the “aspartate aminotransferase [AST]-to-platelet ratio index”, “APRI”, and the “fibrosis index based on four factors”, “FIB-4”, based on age, AST, alanine aminotransferase and platelet count) may also be applicable to chronic HBV infection. The findings are disappointing, with both scoring systems demonstrating poor positive and negative predictive values for advanced fibrosis in comparison to liver histology, both at baseline and after antiviral therapy. In particular, 81% to 89% of patients with advanced fibrosis had lower scores than proposed cut-off thresholds, while 71% of those without clinically significant fibrosis had scores higher than proposed cut-off thresholds. Neither the APRI nor FIB-4 scores have a role in staging hepatic fibrosis in patients with chronic HBV infection.

**Reference:** J Hepatol. 2016;64(4):773-80

**Abstract**

**A nationwide survey of hepatitis E viral infection in French blood donors**

**Authors:** Mansuy JM et al.

**Summary:** These researchers used validated assays to determine the prevalence of anti-HEV immunoglobulin G (IgG) and IgM among 10,569 French blood donors living in mainland France and 3 overseas areas. Epidemiological information was collected by questionnaire. The overall IgG seroprevalence rate was 22.4%, varying from 8–86.4%, depending on the geographical area (p<0.001). The presence of anti-HEV IgG was associated with increasing age (p<0.001) and eating pork meat (p=0.03), pork liver sausages (p<0.001), game meat (p<0.01), offal (p<0.001) and oysters (p=0.02). Drinking bottled water was associated with a lower rate of anti-HEV IgG (p=0.02). Overall IgM seroprevalence was 1% (0–4.6%). The frequency of anti-HEV IgM was higher in donors living in a high anti-HEV IgG seroprevalence area (1.9% vs 0.7%; p<0.001) and in those eating pork liver sausage (1.4% vs 0.7%; p<0.01), pâté (1% vs 0.4%; p=0.04) and wild boar (1.3% vs 0.7%; p<0.01).

**Comment:** HEV infection is an important cause of acute hepatitis in endemic areas and can progress to chronicity with rapid progression to cirrhosis in the immunosuppressed. This nationwide serologic study survey adds to existing HEV prevalence data by demonstrating that HEV is endemic in France, with an overall anti-HEV IgG prevalence rate among adult blood donors of 22.4% that varies from region to region. The results are comparable to seroprevalence rates in other European countries, such as Germany (29%) and The Netherlands (27%). Notably, seroprevalence rates in France were found to have increased in recent years, with dietary habits (the consumption of pig, wild boar, deer and rabbits) and the consumption of contaminated water hypothesised to contribute to this trend. Nonetheless, anti-HEV IgG was detected even in the absence of such risk factors, indicating that there remain other currently unidentified modes of HEV transmission, presumably linked to the environment.

**Reference:** Hepatology. 2016;63(4):1145-54

**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.
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References:
Monoclonal anti-Envelope antibody AP33 protects humanized mice against a patient-derived hepatitis C virus challenge

Authors: Desombere I et al.

Summary: This study compared the ability of two broadly reactive mAbs, 3/11 and AP33, to recognise a distinct, but overlapping, epitope in the viral E2 glycoprotein to protect humanised mice from a patient-derived HCV challenge. Neutralising activity was assessed using HCV pseudovirions and cell culture-derived HCV systems expressing multiple patient-derived envelopes and a human liver chimeric mouse model. HCV RNA was readily detected in all control mice challenged with a patient-derived HCV genotype 1b isolate, whereas 3 of 4 mice treated with AP33 were completely protected. In contrast, only 1 of 4 mice treated with 3/11 remained HCV RNA-negative throughout the observation period; viral load in the remaining 3 was the same as that in the control group. Notably, AP33 efficiently neutralised viral variants that escaped the humoral immune response and reinfected the liver graft of transplant patients.

Comment: Previous studies performed in chimpanzees and humanised mice have demonstrated that poly- and monoclonal antibodies (mAbs) can prevent HCV infection in exposed animals. Initial clinical trials, however, proved disappointing. More recently, several new mAbs have been developed that exhibit more potent antiviral activity. This study investigated the sensitivity of patient-derived, genotype 1b HCV to two non-human mAbs (AP33 and 3/11) that target the same conserved region of HCV E2. AP33 was found to have superior virus-neutralising capacity in vitro and was then assessed in vivo using chimeric unknockin-type plasmaminogen activator/severe combined immunodeficient mice. The study is the first to show that the anti-E2 antibody, AP33, can protect such humanised mice from HCV infection. The recent humanisation of mAb AP33 opens the possibility for clinical trials of AP33 for immunoprophylaxis, such as during liver transplantation, where rapid infection of the graft is otherwise inevitable.


Safety and efficacy of ledipasvir/sofosbuvir for the treatment of genotype 1 hepatitis C in subjects aged 65 years or older

Authors: Saab S et al.

Summary: This retrospective analysis reviewed the safety and efficacy of ledipasvir/sofosbuvir by age group (<65 years vs ≥65 years) among 2293 subjects enrolled in 4 open-label phase 3 clinical trials involving treatment with ledipasvir + sofosbuvir + ribavirin for genotype 1 chronic HCV. SVR12, treatment-emergent adverse events, and graded laboratory abnormalities were analysed according to age group. In all 4 trials, 264 patients were ≥65 years of age; 24 were aged ≥75 years. SVR12 was achieved by 97% (1965 of 2029 patients) of the <65-year age group and 98% (n=258) of those aged ≥65 years. The most common adverse events in both age groups that occurred in ≥10% of patients were headache and fatigue. The rate of study discontinuation due to AEs was similar in the two age cohorts. The use of ribavirin in 1042 (45%) patients increased the number of adverse events, treatment-related adverse events, and adverse events leading to study drug modification/interruption, particularly amongst the elderly.

Comment: The elderly population is disproportionately affected by HCV infection, with prevalence rates in persons aged 61–70 years in Japan and Europe ranging up to 12%. Efficacy and safety data regarding direct-acting anti-HCV viral therapy (DAAVT) in older patients are currently lacking. This retrospective analysis, representing the largest reported experience of DAAVT in older patients, addressed this issue in a cohort of 264 patients aged ≥65 years extracted from four large open-label phase 3 clinical trials of sofosbuvir and ledipasvir, with or without ribavirin, for genotype 1 HCV infection conducted in the United States, Europe, and Japan. In comparison to younger patients, those aged ≥65 years were more likely to be cirrhotic but nonetheless demonstrated comparable SVR12 rates (88% and 97%, respectively). The findings suggest that ribavirin-free regimens are preferable in older patients, due to an increased risk of anaemia.


Genetic variation in STAT4 predicts response to interferon-α therapy for hepatitis B e antigen-positive chronic hepatitis B

Authors: Jiang D-K et al.

Summary: For this investigation into whether genetic variation in STAT4 is associated with the response to IFNα therapy, 466 hepatitis B e antigen (HBeAg)-positive patients with chronic HBV received either IFNα-2b (n=224) or pegylated IFNα-2a (n=242) therapy for 48 weeks, followed by an additional 24 weeks of observation. The SVR rate, defined as HBeAg seroconversion combined with HBV DNA level <2000 copies/mL at week 72, was compared among patients with different rs7574865 genotypes. After 48 weeks of treatment and 24 weeks off treatment, SVR rates in the IFNα-2b and pegylated IFNα-2a therapy groups were 30.4% and 28.9%, respectively. Compared with the rs7574865 G/T/T genotype, the GG genotype (a risk factor of chronic HBV and HBeAg-positive HCC) was associated with a significantly reduced SVR rate in both the IFNα-2b treatment group (21.1% vs 37.2%; p=0.01) and the pegylated IFNα-2a group (18.0% vs 41.2%; p=7.4 × 10⁻⁸). In all 466 patients, the SVR rate was approximately half in patients with the GG genotype compared to patients with the GT/GT genotype (19.3% vs 39.1%; p=4.15 × 10⁻⁵). In multivariate logistic regression analysis adjusting for rs7574865 and clinical variables, rs7574865 was the most significant factor for the prediction of SVR.

Comment: A favourable antiviral response to IFN-α is achieved in only a minority of patients with chronic HBV infection. Whereas IL28B gene status predicts response to combination IFN-α and ribavirin in patients with chronic HCV infection, reported associations between IL28B genotype and response to IFN-α in chronic HBV infection are variable. Thus, other host genetic factors warrant assessment in this setting. This study investigated whether a genetic variant in STAT4 (rs7574865), recently found to be associated with both persistence of HBV infection and development of complicating hepatocellular carcinoma, is also predictive of response to IFN-α treatment. The authors found that the GG rs7574865 STAT4 genotype is associated with around a 50% reduction in SVR compared to GT/GT genotype. Assessment for this genotype prior to IFN-α therapy has the potential to identify those chronic HBV patients who are most likely to respond.


Hepatitis C treatment as prevention of viral transmission and liver-related morbidity in persons who inject drugs

Authors: Cousin A et al.

Summary/Comment: Prevalence rates of chronic HCV infection in excess of 60% have been reported in persons who inject drugs (PWID). This French study aimed to estimate the future impacts of improved HCV testing, linkage to care, treatment uptake and treatment availability on HCV transmission and morbidity in PWID in the direct-acting antiviral therapy (DAAVT) era. Modelling suggested that based on current care arrangements and limiting DAAVT to those with ≥F2 fibrosis, HCV incidence in PWID could be reduced from 42.8% to 24.9% after 10 years, with a further reduction to 7% at 10 years, with corresponding reductions in complications of cirrhosis, if treatment was available from F0 and testing, linkage to care and compliance could all be enhanced. Initiation of treatment at an early stage and more effective preventative strategies will each be important if HCV is to be eliminated in PWID over coming years.


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