In this issue:

- A novel immunocompetent animal model for HBV infection
- Elbasvir/grazoprevir in HCV & inherited disorders
- Exploring the mechanism of liver disease progression during HCV
- Ginsenoside Rg3 shows strong anti-HCV activity
- TDF monotherapy for multiple drug-resistant chronic HBV
- Chronic HCV infection increases risk of ESRD
- Underlying mechanisms of protective immunity against HCV
- Visualizing HEV infection in human liver tissue
- Oral antibiotics ameliorate liver inflammation
- ApoE-dependent stimulation of HCV infection

Abbreviations used in this issue:

- ApoE = apolipoprotein E; DAA = direct-acting antiviral
- ESRD = end-stage renal disease; HBV = hepatitis B virus
- HCV = hepatitis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus
- hNTCP = human sodium taurocholate cotransporting polypeptide
- HR = hazard ratio; HSCs = hepatic stellate cells
- HDV = hepatitis D virus; NK = natural killer
- IC50 = half-maximal inhibitory concentration
- SVR12 = sustained virological response at 12 weeks after end of therapy
- TGF = transforming growth factor

Welcome to issue 47 of Hepatitis Research Review.

Amongst the papers in this issue is one from Korean researchers who report that a ginsenoside compound (G-Rg3) strongly inhibits hepatitis C virus (HCV) propagation. Moreover, G-Rg3 reversed mitochondrial damage caused by HCV infection when used in combination with direct-acting antiviral therapy. In another paper, oral antibiotics lowered the intrahepatic accumulation of pro-inflammatory CD14+CD206+ myeloid cells in advanced viral-related liver disease. This finding could point to a new strategy in the management of patients with viral-induced cirrhosis.

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

Kind Regards,

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

Sodium taurocholate cotransporting polypeptide is the limiting host factor of hepatitis B virus infection in macaque and pig hepatocytes

Authors: Lempp FA et al.

Summary: The human sodium taurocholate cotransporting polypeptide (hNTCP) is identified as being a key receptor for hepatitis B virus (HBV) and hepatitis D virus (HDV) entry into human hepatocytes. Disappointingly, complementation of mouse hepatocytes with hNTCP confers susceptibility to HDV but not HBV infection, which has encouraged the search for additional HBV-specific factors. These researchers examined how hNTCP overexpression promotes HBV and HDV infection in primary hepatocytes from mice, rats, dogs, pigs, rhesus macaques, and cynomolgus macaques. Hepatocytes were transduced with adeno-associated viral vectors encoding hNTCP and subsequently infected with HBV. Cells were analysed for Myrcludex B binding, taurocholate uptake, HBV covalently closed circular DNA formation, and expression of all HBV markers. Sodium taurocholate cotransporting polypeptide (NTcp) from the respective species was cloned and analysed for HBV and HDV receptor activity in the Huh7 human hepatoma cell line. hNTCP-overexpressing hepatocytes from mice, rats and dogs were refractory to HBV infection but permitted HDV infection, whereas hepatocytes from macaques (rhesus and cynomolgus) and pigs became fully susceptible to HBV upon hNTCP expression with efficiencies comparable to human hepatocytes.

Comment: The hNTCP is a key receptor for entry of HBV and HDV into human hepatocytes. This study investigated the possible species-specific function of NTCP by studying the potential impact of over-expression of hNTCP on HBV and HDV infection of primary hepatocytes from various animal species. An important finding is that hepatocytes of macaques and pigs become fully susceptible to both HBV and HDV infection when transcomplemented with hNTCP. This observation raises the possibility of developing immunocompetent animal models to facilitate the preclinical assessment of novel immunotherapeutic approaches, including proof-of-concept studies.


Abstract

Follow RESEARCH REVIEW Australia on Twitter now

@ResearchRevAus

Visit https://twitter.com/ResearchRevAus

ZEPATIER™
(elbasvir and grazoprevir)

ZEPATIER IS PBS LISTED FOR CHRONIC HEPATITIS C (HCV) G1 OR G4 INFECTION IN ADULTS†,‡

PLEASE SEE THE PRIMARY ADVERT FOR PBS INFORMATION AND REFER TO THE PRODUCT INFORMATION BEFORE PRESCRIBING.

CLICK HERE FOR ACCESS TO THE APPROVED PRODUCT INFORMATION.

MDS

Copyright © 2017 Merck Sharp & Dohme Corp a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, USA. All rights reserved. Merck Sharp & Dohme (Australia) Pty Limited, Level 1, Building A, 26 Talavera Rd, Macquarie Park, NSW 2113 Australia. INFC-1205645-0001. First issued September 2017. ZEP0130
Elbasvir/grazoprevir for patients with hepatitis C virus infection and inherited blood disorders: a phase III study

Authors: Hézode C et al.

Summary: The multinational C-EDGE IBLD phase 3 study assessed the safety and efficacy of elbasvir and grazoprevir combination therapy in 150 adults with HCV infection and inherited blood disorders (sickle cell anaemia, thalassaemia, or haemophilia A/B or von Willebrand disease). The study randomised 107 patients to immediate treatment with the oral, once-daily, fixed-dose combination of elbasvir and grazoprevir 50 mg/100 mg for 12 weeks (ITG) or to a deferred treatment group (DTG; placebo followed by active treatment; n=52). In the ITG arm, 100 patients (93.5%) achieved SVR12, 6 relapsed, and 1 was lost to follow-up. SVR12 was achieved in 94.7% (18 of 19), 97.6% (40 of 41), and 89.4% (42 of 47) of patients with sickle cell disease, β-thalassaemia, and haemophilia A/B or von Willebrand disease, respectively. Serious adverse events were reported by 2.8% of patients in the ITG arm and by 11.5% of those in the DTG arm. Haemoglobin levels and international normalised ratio values were similar between the elbasvir/grazoprevir and placebo treatment cohorts. Among patients with haemoglobinopathies (sickle cell disease and β-thalassaemia), the on-treatment change in mean haemoglobin levels was similar between those receiving elbasvir/grazoprevir and those receiving placebo.

Comment: Direct-acting antivirals (DAA) for chronic HCV infection have been little studied in patients with inherited blood disorders, such as haemoglobinopathies and haemolytic anaemia. This randomised, phase III study aimed to assess efficacy and safety of combination therapy for 12 weeks with elbasvir, a non-structural (NS) 5A HCV inhibitor and grazoprevir, a NS3/4A HCV inhibitor, in genotype 1, 4 or 6 HCV-infected patients with sickle cell disease, thalassaemia, haemophilia or von Willebrand disease, including those with and without compensated cirrhosis. High efficacy was demonstrated, with an overall sustained virological response rate 12 weeks after treatment completion of 93.5%. The safety profile was similar to that of a placebo. The data add to existing literature pointing to the effectiveness and tolerability of elbasvir and grazoprevir for the treatment of chronic HCV infection.

Ginsenoside Rg3 restores hepatitis C virus-induced aberrant mitochondrial dynamics and inhibits virus propagation

Authors: Kim SJ et al.

Summary: This in vitro investigation into the anti-HCV activity of several ginsenoside compounds identified that ginsenoside Rg3 (G-Rg3) is a strong inhibitor of HCV propagation. G-Rg3 treatment of HCV-infected cells increased HCV core protein-mediated reduction in the expression level of cytosolic p21, required for increasing cyclin-dependent kinase 1 activity, which catalyses Ser616 phosphorylation of dynamin-related protein 1. G-Rg3 also rescued HCV-infected cells from mitophagy.

Comment: Ginseng has long been used as a traditional herbal remedy in Asian medicine, with the ginsenoside compounds in ginseng exerting a range of immunological and pharmacological effects. This study demonstrates that ginsenoside Rg3 (G-Rg3) has antiviral activity against HCV infection. In particular, G-Rg3 opposes HCV-mediated abnormal mitochondrial fission and mitophagy, phenomena that promote persistent HCV infection. G-Rg3 was found to reverse mitochondrial damage caused by HCV infection when used in combination with DAA therapy, supporting the rationale for its use as an adjutive treatment in this setting. Nonetheless, on a cautionary note, G-Rg3 can be readily metabolised to the potentially toxic metabolite, G-RN2, by various bacterial populations in the gastrointestinal tract, raising the possibility that tolerability and efficacy may vary across individual patients depending upon the particular composition of their gut microbiome.
Monotherapy with tenofovir disoproxil fumarate for multiple drug-resistant chronic hepatitis B: 3-year trial

Authors: Lim YS et al.

Summary: Outcomes are reported from 189 patients with HBV-resistance mutations to entecavir (ETV) and/or adefovir, who had been treated with either tenofovir disoproxil fumarate (TDF) alone or in combination with entecavir (TDF+ETV) for 48 weeks, and who agreed to continue TDF monotherapy (TDF-TDF group) or to switch to TDF monotherapy (TDF+ETV-TDF group) for up to 144 weeks. The primary efficacy endpoint, serum HBV DNA <15 IU/mL at week 48, was achieved by similar proportions of patients in each treatment group (66.3% of the TDF-TDF group and 50.8% of the TDF+ETV-TDF group, p=0.39). At week 144, the proportion with HBV DNA <15 IU/mL was significantly increased from week 48 to 74.5% (p=0.03), with no significant between-group difference (p=0.46). Transient virological breakthrough occurred in 6 patients, which was due to poor drug adherence. At week 144, results of genotypic resistance analysis performed for 19 patients who had HBV DNA levels >60 IU/mL revealed that 6 had <1 detectable HBV resistance mutation, all of which were present at baseline. No cases of additional resistance mutations were reported during study treatment.

Comment: Persistent replication of HBV is an independent risk factor for disease progression to cirrhosis and hepatocellular carcinoma in patients with chronic HBV infection. The reduction in HBV DNA concentrations to very low or undetectable levels by the long-term use of nucleos(ide) analogue therapy is associated with reduced risk of hepatocellular carcinoma development and mortality. Previous studies have demonstrated that combination therapy with TDF for 48 weeks is as efficacious as combination TDF plus entecavir therapy in patients with documented resistance to entecavir and adefovir dipivoxil. This trial aimed to establish the safety and efficacy of prolonged TDF monotherapy for up to 144 weeks in this circumstance as an extension of previous analyses. The findings indicate that prolong TDF monotherapy is well tolerated and gradually increases the rate of virological response, with no additional development of resistance but rather a marked reduction in detectable resistance mutations of HBV. Taken together, TDF monotherapy appears an appropriate long-term treatment option for patients with entecavir- and adefovir dipivoxil-resistant chronic HBV infection.


Hepatitis C viral load, genotype, and increased risk of developing end-stage renal disease: REVEAL-HCV study

Authors: Lai TS et al.

Summary: This Taiwanese community-based prospective cohort study sought to determine whether HCV RNA level and genotype are independent risk factors for developing end-stage renal disease (ESRD). The study enrolled 19,084 participants aged 30–65 years between 1991 and 1992. After a median 16.8-years of follow-up, 204 ESRD events had occurred during 319,474 person-years. The incidence rates of ESRD for monochronically HCV-infected and chronically HCV-infected patients were 60.2 and 194.3 per 100,000 person-years, respectively. In a comparison of patients with and without chronic HCV infection, patients with low and those with high HCV RNA levels had a higher risk of developing ESRD, the multivariable-adjusted hazard ratio was 2.33 (95% CI, 1.40 to 3.89). Compared with patients who did not have chronic HCV infection, patients with low and those with high HCV RNA levels had a higher risk of developing ESRD (HR 2.11; 95% CI, 1.16 to 3.86, and HR 3.06; 95% CI, 1.23 to 7.58; p=0.01), which was due to poor drug adherence. At week 144, results of genotypic resistance analysis performed for 19 patients who had HBV DNA levels >60 IU/mL revealed that 6 had <1 detectable HBV resistance mutation, all of which were present at baseline. No cases of additional resistance mutations were reported during study treatment.

Comment: Persistent replication of HBV is an independent risk factor for disease progression to cirrhosis and hepatocellular carcinoma in patients with chronic HBV infection. The reduction in HBV DNA concentrations to very low or undetectable levels by the long-term use of nucleos(ide) analogue therapy is associated with reduced risk of hepatocellular carcinoma development and mortality. Previous studies have demonstrated that combination therapy with TDF for 48 weeks is as efficacious as combination TDF plus entecavir therapy in patients with documented resistance to entecavir and adefovir dipivoxil. This trial aimed to establish the safety and efficacy of prolonged TDF monotherapy for up to 144 weeks in this circumstance as an extension of previous analyses. The findings indicate that prolong TDF monotherapy is well tolerated and gradually increases the rate of virological response, with no additional development of resistance but rather a marked reduction in detectable resistance mutations of HBV. Taken together, TDF monotherapy appears an appropriate long-term treatment option for patients with entecavir- and adefovir dipivoxil-resistant chronic HBV infection.


Visualization of hepatitis E virus RNA and proteins in the human liver

Authors: Lenggenhager D et al.

Summary: These researchers describe their method for visualising hepatitis E virus (HEV) infection in liver tissue sections. They evaluated a panel of 12 different antibodies against HEV open reading frame (ORF) 1-3 proteins stained for immunohistochemistry (IHC) and two probes for in situ hybridization (ISH) in formalin-fixed, paraffin-embedded (FFPE) HuH7 cells transfected with HEV ORF1-3 expression vectors. They applied IHC (and partly ISH) to Hep293TT cells replicating infectious HEV and liver specimens from 20 patients with HEV infection and 134 healthy controls. ORF1-3 antibodies were detected in all liver specimens of patients with HEV infection and in 6 of 134 healthy controls. For liver tissue as a potentially helpful addition to currently available HEV diagnostics, particularly in countries with low prevalence of HAV and HEV infection at high levels of viraemia but only a problematic 6% sensitivity at low levels of viraemia, such that negative testing of liver tissue by this methodology cannot reliably be taken to exclude HEV infection.

Comment: Although mostly asymptomatic, HEV is the leading cause of acute viral hepatitis worldwide. Diagnosis is made by the detection of anti-HEV antibodies in peripheral blood and HEV RNA in blood or stool, the latter using PCR methodology. Serological testing is often not sufficient, given the high underlying rates of anti-HEV-IGG seropositivity of up to 20%, even in developed countries, and suboptimal sensitivity and specificity of anti-HEV-IGM assays. Furthermore, PCR testing for HEV can be problematic as assays show variable sensitivity and lack standardisation, while HEV viraemia and falciparum malaria co-exist in many countries, making testing during this limited time period. Here, the authors developed an IHC staining technique to detect HEV in liver tissue as a potentially helpful addition to currently available HEV diagnostics, particularly in high-risk patients. This technique is not well characterized in clinical settings in which liver tissue becomes available for testing. Nonetheless, sensitivity was not ideal. In particular, compared to an established PCR method for HEV detection, the IHC analysis was found to have 70% sensitivity for HEV infection at high levels of viraemia but only a problematic 6% sensitivity at low levels of viraemia, such that negative testing of liver tissue by this method cannot reliably be taken to exclude HEV infection.

Reference: J Hepatol. 2017;67(3):462-70

Hepatitis B 80(T) and multiple HLA-BW4 copies combined with KIR3DL1 associate with spontaneous clearance of HCV infection in people who inject drugs

Authors: Thoms C et al.

Summary: Natural killer (NK) cell function is regulated by inhibitory and activating receptors including killer cell immunoglobulin-like receptors (KIRs). These researchers assessed the impact of different genetic KIR/KIR-ligand combinations on the outcome of HCV infection in people who inject drugs (PWID). HLA class I alleles with the Bw4 80(T) motif or multiple copies of HLA-Bw4 alleles in combination with its receptor KIR3DL1 were associated with a protective state against chronic HCV infection in a cohort of 266 PWID from Germany and confirmed in a North American cohort of 342 anti-HCV-positive PWID. In multivariable logistic regression analysis, KIR3DL1/HLA-Bw4 80(T) was associated with spontaneous clearance of HCV infection in PWID, which was confirmed in the PWID cohort from North America. Compared with PWID with detectable HCV RNA, the frequency of individuals with multiple HLA-Bw4 alleles was significantly higher in anti-HCV-positive PWID with resolved HCV infection (29.7% vs 15.2%; p=0.0229) and in anti-HCV seronegative PWID (39.2%, p=0.0006). KIR3DL1 NK cells from HLA-Bw4 80(T)-positive PWID showed superior functional activity compared to HLA-Bw4 80(T)-negative PWID. This differential functionality of KIR3DL1 NK cells in the presence of HLA-Bw4 80(T) and Bw4 80(I) was not observed in healthy donors.

Comment: The natural killer (NK) cell arm of the innate immune system is regulated by a complex network of genetically-determined receptor-ligand pairs. In this study, the authors identified a particular set of NK receptor and ligand genes that confer increased functionality to NK cells and improved outcomes following HCV exposure in a high-risk group injecting parenteral drugs. In particular, analysis of a cohort in Germany demonstrated that HLA class I alleles with the Bw4 80(T) motif or multiple copies of HLA-Bw4 alleles in combination with its receptor KIR3DL1 are associated with protection against chronic HCV infection in such subjects. The findings were confirmed in a second cohort recruited in North America. The study adds to existing literature that points to an important role of NK cells in determining outcome of HCV infection and emphasise, in particular, the beneficial effect of the interaction between the KIR3DL1 receptor and its ligand, HLA-Bw4.

Reference: J Hepatol. 2017;67(3):462-70

ABSTRACT

A RESEARCH REVIEW Publication

www.researchreview.com.au
Intrahepatic CD206+ macrophages contribute to inflammation in advanced viral-related liver disease

Authors: Tan-Garcia A et al.

Summary: This paper describes how intrahepatic CD14+ myeloid cells contribute to chronic liver inflammation in patients with viral-related liver disease. The researchers performed detailed phenotypic, molecular and functional analyses on intrahepatic CD14+ myeloid cells from 19 healthy donors and 15 patients with viral-related liver cirrhosis (HBV, HBV/HDV or HCV). In unsupervised analysis of multi-parametric data, liver disease was associated with the intrahepatic expansion of activated myeloid cells mainly consisting of pro-inflammatory CD14+HLA-DR+CD206+ cells, which spontaneously produced tumour necrosis factor-alpha (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF). These cells only showed heightened pro-inflammatory responses to bacterial toll-like receptor (TLR) agonists and were more refractory to endotoxin-induced tolerance. A liver-specific enrichment of CD14+HLA-DR+CD206+ cells was also detected in a humanised mouse model of liver inflammation. Oral antibiotics lowered the intrahepatic accumulation of pro-inflammatory CD14+CD206+ myeloid cells.

Comment: Mechanisms by which chronic liver inflammation is maintained in patients with viral-mediated cirrhosis are not well understood. Here, the authors investigated the contribution of intrahepatic CD14+ myeloid cells to this phenomenon. They found that livers of such patients were infiltrated with activated myeloid cells, in particular CD14+HLA-DR+CD206+ cells, that spontaneously produced pro-inflammatory mediators and showed both increased responses to stimulation by bacterial products and a higher resistance to lipopolysaccharide tolerance compared to CD14+CD206- myeloid cells. Treatment with oral antibiotics normalised intrahepatic CD14+HLA-DR+CD206+ cell numbers in an HBV-infected humanised mouse model. Taken together, the findings suggest that liver inflammation in advanced, viral-related chronic liver disease can be sustained by a pathological interaction between intrahepatic CD14+HLA-DR+CD206+ myeloid cells and bacterial products derived from the intestine and that strategies to interrupt this harmful interaction should be given additional focus in the management of patients with viral-induced cirrhosis.

Reference: J Hepatol. 2017;67(3):490-500

Maturation of secreted HCV particles by incorporation of secreted ApoE protects from antibodies by enhancing infectivity

Authors: Bankwitz D et al.

Summary/Comment: HCV replication is influenced by host factors and cellular pathways involved in lipid metabolism and remodelling, such as apolipoprotein E (ApoE), which facilitates virus attachment. Direct interactions between ApoE and HCV proteins, including non-structural protein 5A and envelope proteins 1 and 2, have been well described, while lack of ApoE expression is known to prevent assembly of infectious viral progeny after the envelopment of capsids. This study investigated whether ApoE released from non-infected cells interacts with and modulates secreted HCV particles. The findings demonstrate that physiological levels of ApoE released from hepatocytes enhance HCV particle infectivity across all HCV genotypes by incorporating into virus particles, both enhancing interactions with cellular heparin sulphate proteoglycans and facilitating evasion from neutralising antibodies. Strategies to interfere with this ApoE/HCV interaction may be useful both to limit HCV infectivity and increase the efficacy of any future prophylactic HCV vaccines to limit the global impact of HCV infection.

Reference: J Hepatol. 2017;67(3):480-9

Abstract

In chronic HCV

ZEPATIER: POWER AND SIMPLICITY*

FOR G1 PATIENTS*

*95% of treatment-naive G1 and G4 patients achieved SVR12 (cure) with a single once-daily tablet, based on pooled data from a robust clinical program.†

MORE INFORMATION ON ZEPATIER CAN BE ACCESSED FROM WWW.MYMSD.COM.AU


BEFORE PRESCRIBING, PLEASE REVIEW THE PRODUCT INFORMATION. CLICK HERE FOR ACCESS TO THE PRODUCT INFORMATION.

Reference: 1. ZEPATIER Approved Product Information, 31 May 2017

Copyright © 2017 Merck Sharp & Dohme Corp a subsidiary of Merck & Co. Inc. Kenilworth, New Jersey, USA. All rights reserved.

Merck Sharp & Dohme (Australia) Pty Limited, Level 1, Building A, 26 Talavera Rd, Macquarie Park, NSW 2113 Australia.


Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.

Research Reviews are prepared with an independent commentary from relevant specialists. To become a reviewer please email geoff@researchreview.com.au

Research Reviews Australia Pty Ltd is an independent Australian publisher. Research Review receives funding from a variety of sources including government departments, health product companies, insurers and other organisations with an interest in health. Journal content is created independently of sponsor companies with assistance from leading local specialists. Privacy Policy: Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time. Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

Research Review publications are intended for Australian health professionals.

www.researchreview.com.au

a RESEARCH REVIEW publication

© 2017 RESEARCH REVIEW

Hepatitis Research Review™