Natural killer cell phenotype modulation and natural killer/T-cell interplay in nucleos(t)ide analogue-treated hepatitis e antigen-negative patients with chronic hepatitis B

Authors: Berti C et al.

Summary: This investigation examined natural killer (NK) cell phenotype and function in hepatitis B e antigen (HBeAg)-negative chronic hepatitis B virus (HBV) infection: 25 enrolled patients were untreated and 46 received nucleos(t)ide analogue therapy (36 HBsAg+ and 10 HBsAg- HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HCV = hepatitis C virus; HCV = hepatitis B virus; IFN = interferon; NK = natural killer.

Comment: It is well established that HBV infection in pregnancy is associated with both an increased risk of acute liver failure (ALF) and worse maternal and foetal outcomes than occur with other aetiologies of acute viral hepatitis, although responsible mechanisms are not clear. This novel, prospective study of innate immunity in patients with genotype 1 HBV infection found that, despite an increased number of peripheral blood monocytes/macrophages, downstream Toll-like receptor (TLR) signalling in peripheral blood monocytes/macrophages is reduced in ALF due to a range of aetiologies, but more markedly so when due to HEV infection, further pointing to a dominant inhibitory effect of HEV on innate immunity that may promote viral persistence and poor outcomes, especially in pregnancy.


Impaired monocyte-macrophage functions and defective Toll-like receptor signaling in hepatitis E virus-infected pregnant women with acute liver failure

Authors: Sehgal R et al.

Summary: These researchers sought to determine the role of monocytes and macrophages (mono-macs) in the pathogenesis of acute hepatitis E virus (HEV) infection and development of acute liver failure in pregnancy. Mono-macs functionality was examined in 44 pregnant versus 10 non-pregnant women with acute viral hepatitis due to HEV infection, 12 pregnant versus 5 non-pregnant women with acute liver failure due to HEV infection, and 20 healthy pregnant controls versus 10 healthy nonpregnant controls. The study also recruited 5 pregnant and 12 non-pregnant women with non-HEV-related acute liver failure. Frequency of mono-macs and dendritic cells was increased during HEV infection compared to healthy controls (p<0.001). Macrophages were increased (p<0.002) in HEV-infected pregnant women with acute liver failure compared to pregnant women with non-HEV-related acute liver failure. Flow cytometry analysis revealed significantly impaired macrophage phagocytic activity and Escherichia coli-induced reactive oxygen species production in pregnant HEV-infected women with acute liver failure compared to pregnant HEV-infected women with acute viral hepatitis (p<0.001), non-HEV-infected women with acute liver failure, and pregnant women with non-HEV-related acute liver failure (p<0.02). Toll-like receptor (TLR3 and TLR4 expression and downstream MYD88 signalling molecules IRF3 and IRF7 were significantly down-regulated in pregnant women with HEV-related acute liver failure (p<0.00) compared to pregnant women with either HEV-related acute viral hepatitis or non-HEV-related acute liver failure.

Comment: It is important to note that HEV infection in pregnancy is associated with both an increased risk of acute liver failure (ALF) and worse maternal and foetal outcomes than occur with other aetiologies of acute viral hepatitis, although responsible mechanisms are not clear. This novel, prospective study of innate immunity in patients with genotype 1 HBV infection found that, despite an increased number of peripheral blood monocytes/macrophages, downstream Toll-like receptor (TLR) signalling in peripheral blood monocytes/macrophages is reduced in ALF due to a range of aetiologies, but more markedly so when due to HEV infection, further pointing to a dominant inhibitory effect of HEV on innate immunity that may promote viral persistence and poor outcomes, especially in pregnancy.


Abbreviations used in this issue:

DAA = direct acting antiviral; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HCV = hepatitis C virus; HCV = hepatitis B virus; IFN = interferon; NK = natural killer.
Validation of hepatitis B virus-related hepatocellular carcinoma prediction models in the era of antiviral therapy

Authors: Jung KS et al.

Summary: This study analysed data from 1,308 patients (median age 50 years) with chronic HBV infection; 848 patients were receiving antivirals and 460 were not. At baseline, liver stiffness was noninvasively measured by transient elastography in all participants. The study researchers assessed the performances of conventional hepatocellular carcinoma (HCC) prediction models (CU-HCC, GAG-HCC, REACH-B, and LSM-HCC scores) and the modified REACH-B (mREACH-B) score, in which liver stiffness values are incorporated into the REACH-B score instead of serum HBV DNA levels. During a median 75.3 months of follow-up, HCC developed in 125 (9.6%) patients. mREACH-B score had the highest areas under the receiver operating characteristic curves (AUROC) for the prediction of HCC development at 3 and 5 years (0.828 and 0.806), compared with LSM-HCC (0.777 and 0.759), GAG-HCC (0.751 and 0.757), and REACH-B (0.717 and 0.699) and CU-HCC (0.698 and 0.700) scores, respectively (all p values < 0.05 vs mREACH-B). When serum HBV DNA levels were excluded from the formula for REACH-B score, AUROCs for HCC development at 3/5 years improved paradoxically (from 0.717/0.699 to 0.757/0.732, respectively). Among antiviral-treated patients, mREACH-B score had superior prognostic performance for HCC development at 3 and 5 years, compared to other prediction models. However, in the cohort without antiviral therapy, mREACH-B score had similar prognostic performance to those of other prediction models.


Abstract

HCV vertical transmission in pregnancy: New horizons in the era of DAAs

Authors: Kanninen TT et al.

Summary/Comment: Much recent interest has centred on the use of tenofovir in the third trimester of pregnancy, whereas there was only a slight decline in middle-aged adults (annual percent change: –2%, 2003–2011) and in adolescents and young adults (annual percent change: 0.04%, 2003–2011). From 2003 to 2010, the incidence of HCC declined amongst children (annual percent change: –16.6%, 2003–2010), adolescents and young adults (annual percent change: –7.9%, 2003–2011). The incidence rate of HCC in children fell to zero in 2011, whereas there was only a slight decline in middle-aged adults (annual percent change: 2%, 2003–2011) and a slight upward trend was observed in the elderly (1.3%), particularly in women (1.7%).


Abstract

Changing incidence patterns of hepatocellular carcinoma among age groups in Taiwan

Authors: Hung GY et al.

Summary: This article reports on changes in HCC age-specific incidence patterns in Taiwan following the launch in 1984 of a universal HBV immunisation programme. Data from the population-based Taiwan Cancer Registry revealed that 82,856 patients were diagnosed with HCC between 2003 and 2011, yielding an age-standardised incidence rate of 32.97 per 100,000 person-years. HCC was primarily diagnosed in middle-aged adults (50.1%) and the elderly (49.1%), whereas incidence rates were very low in children (0.04%) and adolescents and young adults (0.8%). From 2003 to 2010, the incidence of HCC declined amongst children (annual percent change: ~16.6%, 2003–2010), adolescents and young adults (annual percent change: ~7.9%, 2003–2011). The incidence rate of HCC in children fell to zero in 2011, whereas there was only a slight decline in middle-aged adults (annual percent change: ~2%, 2003–2011) and a slight upward trend was observed in the elderly (1.3%), particularly in women (1.7%).

Reference: J Hepatol. 2015;63(6):1314-22

Abstract

Early inhibition of hepatocyte innate responses by hepatitis B virus

Authors: Luangsay S et al.

Summary: These researchers sought to determine whether early interactions between HBV viral particles and hepatocyte innate immune responses influence the outcome of HBV infection. They exposed the HepaRG cell line and primary human hepatocytes to HBV, delivered either by a physiological route or baculovirus vector (Bac-HBV), and analysed changes in expression of selected antiviral/pro-inflammatory cytokines and interferon (IFN)-stimulated genes over the subsequent 24h. There was evidence of hepatocytes detecting HBV and expressing innate genes when exposed to either HBV virions or Bac-HBV. Whereas Bac-HBV triggered a strong antiviral cytokine secretion followed by the clearance of replicative intermediates, physiological exposure to HBV induced an abortive response. The early inhibition of innate response by HBV was observed predominantly in TLR3 and RIG-I/MDA5 signalling pathways in the presence of an exogenous agonist, leading to a decreased expression of several pro-inflammatory and antiviral cytokine genes. This early inhibition of dsRNA-mediated response was found to be due to factor(s) present in the HBV inoculum, which are not HBsAg or HBcAg and do not require de novo viral protein synthesis and replication.

Comment: This novel study employed a human hepatocyte cell line (HepaRG) to examine the early interplay between HBV and hepatocytes and, in particular, mechanisms that might facilitate development of chronic HBV infection. Consideration of pro-inflammatory gene expression indicates that hepatocytes can initiate a very early antiviral immune response to HBV. However, within 2 hours of viral exposure, and in the absence of de novo viral synthesis, both TLR3 and retinoic acid-inducible protein (RIG)-1/melanoma differentiation-associated gene (MDA) 5-mediated innate immune responses in hepatocytes are suppressed by mechanisms that correlate with the development of persistent HBV infection. Future identification of the precise molecular events leading to inhibition of hepatocellular innate immunity very early after HBV exposure may permit new treatment strategies, in addition to current approaches based on suppression of viral replication.

Reference: J Hepatol. 2015;63(6):1314-22

Independent commentary by Professor Stephen Riordan.

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References:

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References:
A cell culture system for distinguishing hepatitis C viruses with and without liver cancer-related mutations in the viral core gene

Authors: El-Shamy A et al.

Summary: These researchers explain that patients with genotype 1b HCV infection with O° and/or M° core gene mutations have an almost 5-fold increased risk of developing HCC and increased insulin resistance, but there is no suitable experimental system enabling direct comparison of the effects of these mutations on cellular gene expression. They describe how they developed a cell-based system for testing high-risk and control HCV viruses. Long-term treatment of HuH7 cells with human serum resulted in growth-arrested, hepatocyte-like cells with gene profiles that overlapped significantly with that of primary human hepatocytes. High-risk (O°/M°) and control (R°/L°) viruses had dramatically different effects on gene expression of these cells. Whereas the high-risk virus enhanced expression of pathways associated with cancer and type 2 diabetes, the control virus enhanced pathways associated with oxidative phosphorylation. When profiles of infected cells were compared to those of liver biopsies from 216 patients with early-stage HCV-related cirrhosis followed for up to 23 years, a significant correlation was observed between the transcriptome of cells replicating the high-risk virus and an HCC high-risk profile in patients (p=0.03), whereas no such association was observed for non-HCC-related clinical outcomes.

Comment: HCV-related HCC continues to be diagnosed at an unfortunately late stage in a substantial proportion of cases, with only 12% of such patients in the United States being identified by surveillance, according to a contemporary analysis. Identification of viral factors conferring increased HCC potential may focus attention on more effective surveillance strategies in those at particularly increased risk. This study, performed using a novel cell culture system based on HuH7 cells maintained long-term in media containing human serum, provides the first direct evidence for the oncogenic effects of point mutations in the HCV core gene, first suggested by clinical and epidemiological studies. Patients harbouring HCV variants exhibiting these mutations, in particular, may benefit most from surveillance strategies designed to detect HCC at an early, and hence treatable, stage.

Reference: J Hepatol. 2015;63(6):1323-33

Abstract

Hypoxia impairs anti-viral activity of natural killer (NK) cells but has little effect on anti-fibrotic NK cell functions in hepatitis C virus infection

Authors: Wolter F et al.

Summary: Outcomes are reported from experiments in which peripheral (n=34) and intrahepatic (n=15) NK cells from HCV+ patients as well as circulating NK cells from healthy donors (n=20) were evaluated for antiviral and antifibrotic activity via co-culture experiments with HuH7 replication cells and hepatocyte stellate cells, respectively. Antiviral activity of resting NK cells from healthy controls was affected by hypoxia but was not significantly reduced by hypoxia significantly reduced the response of healthy NK cells to cytokine stimulation. In contrast to healthy controls, resting and cytokine-activated peripheral NK cells from HCV patients exhibited significantly lower antiviral activity than controls was not affected by hypoxia. However, hypoxia significantly reduced the response of activated peripheral NK cells from HCV patients. When profiles of infected cells were compared to those of liver biopsies from 216 patients with early-stage HCV-related cirrhosis followed for up to 23 years, a significant correlation was observed between the transcriptome of cells replicating the high-risk virus and an HCC high-risk profile in patients (p=0.03), whereas no such association was observed for non-HCC-related clinical outcomes.

Comment: An effective antiviral NK cell response is important for clearance of HCV infection. NK cells also play an important antifibrotic role via a cytotoxic effect on activated hepatic stellate cells. However, existing data have been derived from analyses performed under atmospheric oxygen conditions (20% oxygen). Given that the hepatic microenvironment is considerably hypoxic, with a median oxygen tension in the order of only 5% oxygen and lower still in the setting of inflammation, an important question is whether such low oxygen concentrations may have any effect on the antiviral and antifibrotic activities of NK cells. This study is therefore important in demonstrating that the antiviral, but not antifibrotic, effect of NK cells is substantially impaired by hypoxia (low normoxia), especially in the setting of HCV infection. The findings further current understanding of NK cell functions expected to be operative in the liver under physiological and pathological conditions in vivo.

Reference: J Hepatol. 2015;63(6):1334-44

Abstract

TG1050, an immunotherapeutic to treat chronic hepatitis B, induces robust T cells and exerts an antiviral effect in HBV-persistent mice

Authors: Martin P et al.

Summary: This paper describes results of in vitro and in vivo studies that assessed the ability of TG1050, a novel immunotherapeutic, to induce functional T cells under conditions of chronic HBV infection. In in vitro studies, TG1050 expressed an over length polyprotein together with the dominant S gene product. Following AAV-mediated administration in primates, TG1050 induced robust, multi-specific and long-lasting HBV-specific T cells that remained detectable up to 1 year post-injection. These results targeted all 3 encoded immunogens and displayed bi-functionality (i.e. capacity to produce both IFN-γ and TNF-α as well as cytolytic functions). Moreover, there were significant reductions in circulating levels of HBV DNA and HbsAg, while alanine aminotransferase levels remained in the normal range.

Comment: Patients who spontaneously resolve acute HBV exposure typically display broad and potent CD4+ and CD8+ T cell responses against multiple HBV antigens. Among possible new approaches to management of chronic HBV infection are HBV-specific immunotherapies aimed at inducing immune responses that mirror those that promote spontaneous viral clearance. Such immunotherapeutics developed to date have included only one or two HBV antigens and demonstrate only limited clinical efficacy. The immunotherapeutic agent developed for this study (TG1050) is novel in that it is based on a non-replicating adenovirus vector encoding an unique fusion protein comprising either full length pre-S2 (including pre-S1 domains of both the pre-S1 and pre-S2 cleavage products, polyomavirus, and envelope). Mice vaccinated by a single application of TG1050 developed a vigorous CD8+ T cell and cytokine response that was accompanied on occasion by a reduction in serum HBV DNA and HbsAg levels. Clinical experience is awaited.

Reference: Gut. 2015;64(12):1961-71

Abstract

Association between level of hepatitis D virus infection at week 24 of pegylated interferon therapy and outcome

Authors: Keskin O et al.

Summary: Data were analysed for this investigation from 50 patients with compensated liver disease who tested positive for anti-hepatitis D virus (HDV) and HDV RNA, and who participated in the Hep-Net-International Delta Hepatitis Intervention Trial. These researchers aimed to identify factors associated with outcomes of pegylated interferon (Peg-IFN) treatment, with and without adefovir dipixol. Study treatment regimens consisted of Peg-IFN α-2a, with adefovir or placebo, or adefovir dipivoxil alone, for 48 weeks. Twenty-four weeks after treatment ended, 41 patients were evaluated for levels of HDV RNA and DNA, liver enzymes, and HbsAg. Based on univariate and multivariate analysis, the level of HDV RNA at week 24 of treatment was associated more strongly with response to therapy than any other factors that were analysed. HbsAg levels at week 24 of treatment were associated with a response to therapy only in univariate analysis. Lack of HDV RNA at week 24 of treatment identified non-responders with a response to treatment only in univariate analysis. In multivariate analysis, HDV RNA at week 24 of treatment identified non-responders with a response to treatment only in multivariate analysis. HbsAg levels identified non-responders with a response to treatment only in multivariate analysis.

Comment: The only currently available therapy for chronic HDV infection is pegylated-IFNα (Peg-IFNα). This study prospectively assessed efficacy of 48 weeks of Peg-IFNα, with or without adefovir dipivoxil, in chronic HDV infection. Sustained virological response (SVR), defined by undetectable HDV RNA in peripheral blood at post-treatment week 24, occurred in 16/38 (42%) patients with available data. Undetectable HDV RNA at week 24 of treatment was found to have a positive predictive value of 100% for SVR. However, subsequent virological relapse occurred in over 56% of patients who achieved “SVR”, indicating that, in stark contrast to the situation with chronic HCV infection, virological status at post-treatment week 24, at least as assessed using currently available HDV RNA assays, is not reliably predictive of virological cure. Whether treatment should be extended beyond 48 weeks to improve long-term outcome is currently unknown.


Abstract