Glecaprevir and Pibrentasvir in Patients with HCV and Severe Renal Impairment.

BACKGROUND: Chronic hepatitis C virus (HCV) infection is more prevalent among patients who have chronic kidney disease than among those who do not have the disease. Patients with chronic kidney disease who also have HCV infection are at higher risk for progression to end-stage renal disease than those who have chronic kidney disease without HCV infection. Patients with both HCV infection and advanced chronic kidney disease have limited treatment options.

METHODS: We conducted a multicenter, open-label, phase 3 trial to evaluate the efficacy and safety of treatment with the combination of the NS3/4A protease inhibitor glecaprevir and the NS5A inhibitor pibrentasvir for 12 weeks in adults who had HCV genotype 1, 2, 3, 4, 5, or 6 infection and also had compensated liver disease (with or without cirrhosis) with severe renal impairment, dependence on dialysis, or both. Patients had stage 4 or 5 chronic kidney disease and either had received no previous treatment for HCV infection or had received previous treatment with interferon or pegylated interferon, ribavirin, sofosbuvir, or a combination of these medications. The primary end point was a sustained virologic response 12 weeks after the end of treatment.

RESULTS: Among the 104 patients enrolled in the trial, 52% had genotype 1 infection, 16% had genotype 2 infection, 11% had genotype 3 infection, 19% had genotype 4 infection, and 2% had genotype 5 or 6 infection. The sustained virologic response rate was 98% (102 of 104 patients; 95% confidence interval, 95 to 100). No patients had virologic failure during treatment, and no patients had a virologic relapse after the end of treatment. Adverse events that were reported in at least 10% of the patients were pruritus, fatigue, and nausea. Serious adverse events were reported in 24% of the patients. Four patients discontinued the trial treatment prematurely because of adverse events; three of these patients had a sustained virologic response.

CONCLUSIONS: Treatment with glecaprevir and pibrentasvir for 12 weeks resulted in a high rate of sustained virologic response in patients with stage 4 or 5 chronic kidney disease and HCV infection. (Funded by AbbVie; ClinicalTrials.gov number, NCT02651194.).

Ledipasvir and Sofosbuvir for untreated HCV genotype 1 infection in end stage renal disease patients: A prospective observational study.
Surendra M1, Raju SB1, Sridhar N1,
INTRODUCTION: Hepatitis C virus (HCV) infection in end stage renal disease (ESRD) is associated with increased mortality. Recently, numerous directly acting antiviral agents have been approved for the management of HCV. Ledipasvir along with Sofosbuvir has been approved for management of genotype 1 infection in patients with eGFR ≥30 mL/min. However, there is paucity of data regarding its role in the management of patients on dialysis.

MATERIAL AND METHODS: This is a single center prospective open label observational study to assess the safety and efficacy of Ledipasvir and Sofosbuvir in hemodialysis (HD) patients who were diagnosed with HCV genotype 1 infection. Eligibility criteria were treatment naive HD patients with normal liver histology. We administered Ledipasvir and Sofosbuvir combination tablet on alternate days for a period of 12 weeks. Primary efficacy end point was the assessment of sustained virological response (SVR12), and the safety end point was the discontinuation of therapy secondary to adverse drug effects.

RESULTS: A total of 21 patients were treated with this regimen. Two patients expired during the study period and are not related to the therapy. SVR12 was achieved in all the 19 patients. None of the patients in our study discontinued the therapy or had severe adverse drug effects. One patient had head ache and another patient had giddiness which were managed symptomatically.

CONCLUSION: Ledipasvir and Sofosbuvir combination therapy on alternate days, is effective even in ESRD patients, with excellent SVR12 rates, and it is as safe as in other population groups, without any major adverse reactions.

OBJECTIVES: Hepatitis C genotype 6 (HCV-GT6) is one of the most prevalent genotypes in Southeast Asia. Ledipasvir and sofosbuvir fixed-dose combination (LDV/SOF FDC) for 12 weeks has been shown to be effective for multiple HCV genotypes including treatment-naive HCV-6. Our goal was to examine treatment outcomes in a diverse HCV-6 population.

METHODS: We prospectively enrolled 60 HCV-GT6 patients at four US centers. Treatment-naive without cirrhosis patients received open-labeled LDV/SOF FDC orally once a day for 8 weeks; All cirrhotic and/or treatment-experienced patients received LDV/SOF FDC for 12 weeks. The primary outcome was sustained virological response 12 weeks after therapy (SVR12). Secondary outcomes were adverse events (AEs) and/or serious adverse events (SAEs). All patients gave written consent. RESULTS: Overall mean age was 58±10 and 58% were male. All patients were Asian and foreign born. The 8-week group included 20 patients (33.3%) and the 12-week included 40 patients (66.7%). There were 2 (5%) patients with decompensation, 3 with liver cancer (7.5%), and 14 with prior treatment (35%) in the 12-week group. SVR12 was 95.0% for the 8-week group (19/20) and 95.0% for the 12-week group (38/40). AEs included fatigue (5%), insomnia (3.3%), headache (1.7%), and nausea (1.7%); however, all patients completed the intended treatment duration. There were two treatment-unrelated SAEs.

CONCLUSIONS: LDV/SOF FDC for 8 or 12 weeks was safe and effective for patients without cirrhosis or prior treatment failure as well as for patients with cirrhosis and/or prior treatment failure, respectively.

**OBJECTIVE:** This study prospectively examined the independent courses of alcohol, drugs, and smoking over 18 months in 154 patients preparing for hepatitis C (HCV) treatment in relation to functioning, negative coping, and satisfaction with quality of life, in data collected from a randomized controlled trial of multiple-family group psychoeducation for patients preparing for HCV treatment. Patients with HCV who had consistent abstinence, consistent use, or achievement of abstinence after study entry were examined for outcomes pertaining to functioning in the context of HCV, negative coping, and satisfaction with quality of life.

**METHODS:** Of 309 patients considering treatment for HCV recruited from outpatient clinics at two major university medical centers and a Veterans Affairs medical center for a randomized controlled trial of a psychoeducation intervention, 154 completed baseline, 6-month, and 18-month assessments. The assessments included structured diagnostic interviews; questionnaires examining functioning, coping, and satisfaction with quality of life; medical record review; and urine testing for substances of abuse. For these analyses, substance use patterns were determined as consistent abstinence, consistent use, and achieving abstinence after study entry, for alcohol and drug use and smoking. **RESULTS:** The entire sample generally improved in all of these three outcomes over the course of the study. The course of alcohol, drugs, and smoking predicted HCV-related functioning, negative coping, and satisfaction with quality of life outcomes over 18 months. Three specific patterns of substance use (consistent abstinence, consistent use, and achievement of abstinence after study entry) of these substances diverged in association with outcomes related to functioning, negative coping, and satisfaction with quality of life, not only across trajectories over time within substance types but also between types of substances.

**CONCLUSIONS:** This study's finding that different substances were associated with distinct clinical outcomes suggests the need to conceptually unbundle different types of substances in managing HCV. Future research is needed to examine the clinical utility of further unbundling of these substances and also to further investigate effects of various amounts of use of these substances.


**BACKGROUND:** Direct acting antiviral (DAA)-based treatment with ombitasvir/paritaprevir/ritonavir ± dasabuvir (OBV/PTV/r ± DSV) is highly effective in HCV genotype 1 or 4 infection and well-tolerated with only few side effects. However, pruritus has been observed in several trials in up to 20% of patients and seems to be unique for this DAA combination. **OBJECTIVES:** The aim of this preliminary study was to investigate the effect of OBV/PTV/r ± DSV on bile acid levels and to correlate them to the emergence of pruritus during treatment. **METHODS:** Twenty patients with chronic hepatitis C genotype 1 or 4 were treated for 12 or 24 weeks with OBV/PTV/r ± DSV with or without ribavirin. Side effects including pruritus were assessed every 4 weeks during treatment or on demand. Blood was collected in fasting state at baseline and at treatment week 4 for determination of bile acid concentrations by high-resolution mass spectrometry. **RESULTS:** Pruritus developed in 5 out of 20 patients during the first 4 weeks of DAA treatment. Pruritus was self-limiting during DAA treatment in 4
patients while one patient required cholestyramine treatment and responded well. Total bile acid levels increased approximately 4 fold by treatment week 4. **CONCLUSIONS:** Pruritus observed during OBV/PTV/r ± DSV treatment of chronic hepatitis C is associated with increased on-treatment serum bile acid levels, possibly due to ritonavir-induced alterations of bile acid transport.

**BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES**


Despite recent advances in therapeutic options, hepatitis C virus (HCV) remains a severe global disease burden, and a vaccine can substantially reduce its incidence. Due to its extremely high sequence variability, HCV can readily escape the immune response; thus, an effective vaccine must target conserved, functionally important epitopes. Using the structure of a broadly neutralizing antibody in complex with a conserved linear epitope from the HCV E2 envelope glycoprotein (residues 412 to 423; epitope I), we performed structure-based design of immunogens to induce antibody responses to this epitope. This resulted in epitope-based immunogens based on a cyclic defensin protein, as well as a bivalent immunogen with two copies of the epitope on the E2 surface. We solved the X-ray structure of a cyclic immunogen in complex with the HCV1 antibody and confirmed preservation of the epitope conformation and the HCV1 interface. Mice vaccinated with our designed immunogens produced robust antibody responses to epitope I, and their serum could neutralize HCV. Notably, the cyclic designs induced greater epitope-specific responses and neutralization than the native peptide epitope.

Beyond successfully designing several novel HCV immunogens, this study demonstrates the principle that neutralizing anti-HCV antibodies can be induced by epitope-based, engineered vaccines and provides the basis for further efforts in structure-based design of HCV vaccines.

**IMPORTANCE:** Hepatitis C virus is a leading cause of liver disease and liver cancer, with approximately 3% of the world's population infected. To combat this virus, an effective vaccine would have distinct advantages over current therapeutic options, yet experimental vaccines have not been successful to date, due in part to the virus's high sequence variability leading to immune escape. In this study, we rationally designed several vaccine immunogens based on the structure of a conserved epitope that is the target of broadly neutralizing antibodies. In vivo results in mice indicated that these antigens elicited epitope-specific neutralizing antibodies, with various degrees of potency and breadth. These promising results suggest that a rational design approach can be used to generate an effective vaccine for this virus.


Our objective was to identify drug interactions between ledipasvir (LDV) and sofosbuvir (SOF) against a genotype 1b replicon to determine optimal exposures for each agent that will maximize antiviral activity against susceptible and drug-resistant subpopulations. LDV and SOF were evaluated using a fully factorial experimental design in the BelloCell system. Replicon levels and drug-resistant variants were quantified at various times post-therapy for 14 days and a high-dimensional mathematical model was fit to the data. Mutations associated with SOF resistance
were not detected; but LDV-resistant mutants were selected and mutant subpopulations increased as exposure intensity increased. Combination therapy was additive for the total replicon population and the LDV-resistant population, but a threshold concentration of 100 ng/ml of SOF must be attained to suppress LDV-resistant subpopulations. These novel findings hold important implications for not only improving therapeutic outcomes, but also maximizing the clinical utility of LDV and SOF combination regimens.


Autophagy plays important roles in maintaining cellular homeostasis. It uses double- or multiple-membrane vesicles termed autophagosomes to remove protein aggregates and damaged organelles from the cytoplasm for recycling. Hepatitis C virus (HCV) has been shown to induce autophagy to enhance its own replication. Here we describe a procedure that combines membrane flotation and affinity chromatography for the purification of autophagosomes from cells that harbor an HCV subgenomic RNA replicon. The purified autophagosomes had double- or multiple-membrane structures with a diameter ranging from 200 nm to 600 nm. The analysis of proteins associated with HCV-induced autophagosomes by proteomics led to the identification of HCV nonstructural proteins as well as proteins involved in membrane trafficking. Notably, caveolin-1, caveolin-2, and annexin A2, which are proteins associated with lipid rafts, were also identified. The association of lipid rafts with HCV-induced autophagosomes was confirmed by Western blotting, immunofluorescence microscopy, and immunoelectron microscopy. Their association with autophagosomes was also confirmed in HCV-infected cells. The association of lipid rafts with autophagosomes was specific to HCV, as it was not detected in autophagosomes induced by nutrient starvation. Further analysis indicated that the autophagosomes purified from HCV replicon cells could mediate HCV RNA replication in a lipid raft-dependent manner, as the depletion of cholesterol, a major component of lipid rafts, from autophagosomes abolished HCV RNA replication. Our studies thus demonstrated that HCV could specifically induce the association of lipid rafts with autophagosomes for its RNA replication.

**IMPORTANCE:** HCV can cause severe liver diseases, including cirrhosis and hepatocellular carcinoma, and is one of the most important human pathogens. Infection with HCV can lead to the reorganization of membrane structures in its host cells, including the induction of autophagosomes. In this study, we developed a procedure to purify HCV-induced autophagosomes and demonstrated that HCV could induce the localization of lipid rafts to autophagosomes to mediate its RNA replication.

This finding provided important information for further understanding the life cycle of HCV and its interaction with the host cells.

**HIV/HCV COINFECTION**


Hepatitis C virus (HCV) cure rates have been similar in patients with and without human immunodeficiency virus (HIV) coinfection; however, in the ION-4 study, black patients treated with ledipasvir/sofosbuvir (LDV/SOF) were significantly less likely to achieve cure (90%) compared to nonblack patients (99%). There are limited real-world data on the effectiveness of
oral direct-acting antivirals (DAAs) in predominantly minority HIV/HCV coinfected populations. We analyzed HCV treatment outcomes among 255 HCV coinfected patients initiating DAAs between February 2014 and March 2016 in an urban clinic in Baltimore, Maryland. To facilitate adherence, patients received standardized HIV nurse/pharmacist support, which included nurse visits and telephone calls. Median age was 43 years, 88% were black, 73% male, 69% had a history of injection drug use, 45% a history of hazardous alcohol use, and 57% a comorbid psychiatric diagnosis. Median CD4 count was 577 (interquartile range, 397-820) cells/mm3; most (97%) were on antiretroviral therapy, had HIV RNA <20 copies/mL (87%), and were infected with HCV genotype 1 (98%). Over 60% had significant fibrosis (Fibrosis-4 Index score 1.45-3.25 [44%] and >3.25 [17%, cirrhosis]) and 30% were HCV treatment experienced. The majority of patients received LDV/SOF with or without ribavirin (91%) and were treated for 12 weeks. Overall, the sustained virological response rate was 97% (95% confidence interval [CI], 93-98) and did not vary by race (black, 96% [95% CI, 93-98]; nonblack, 97%, [95% CI, 83-99]), history of injection drug use, alcohol use, or psychiatric diagnosis. **CONCLUSION:** HCV treatment was highly effective among HIV-infected patients who received care within an integrated nurse/pharmacist adherence support program. These results suggest that race and psychosocial comorbidity may not be barriers to HCV elimination.


**BACKGROUND:** Patients with human immunodeficiency virus (HIV) and/or chronic hepatitis C virus (HCV) infection may be prescribed statins as treatment for metabolic/cardiovascular disease, but it remains unclear if the risk of acute liver injury (ALI) is increased for statin initiators compared to nonusers in groups classified by HIV/HCV status. **METHODS:** We conducted a cohort study to compare rates of ALI in statin initiators vs nonusers among 7686 HIV/HCV-coinfected, 8155 HCV-monoinfected, 17739 HIV-monoinfected, and 36604 uninfected persons in the Veterans Aging Cohort Study (2000-2012). We determined development of (1) liver aminotransferases >200 U/L, (2) severe ALI (coagulopathy with hyperbilirubinemia), and (3) death, all within 18 months. Cox regression was used to determine propensity score-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of outcomes in statin initiators compared to nonusers across the groups. **RESULTS:** Among HIV/HCV-coinfected patients, statin initiators had lower risks of aminotransferase levels >200 U/L (HR, 0.66 [95% CI, .53-.83]), severe ALI (HR, 0.23 [95% CI, .12-.46]), and death (HR, 0.36 [95% CI, .28-.46]) compared with statin nonusers. In the setting of chronic HCV alone, statin initiators had reduced risks of aminotransferase elevations (HR, 0.57 [95% CI, .45-.72]), severe ALI (HR, 0.15 [95% CI, .06-.37]), and death (HR, 0.42 [95% CI, .32-.54]) than nonusers. Among HIV-monoinfected patients, statin initiators had lower risks of aminotransferase increases (HR, 0.52 [95% CI, .40-.66]), severe ALI (HR, 0.26 [95% CI, .13-.55]), and death (HR, 0.19 [95% CI, .16-.23]) compared with nonusers. Results were similar among uninfected persons. **CONCLUSIONS:** Regardless of HIV and/or chronic HCV status, statin initiators had a lower risk of ALI and death within 18 months compared with statin nonusers.

Liver steatosis is common in Human Immunodeficiency Virus (HIV) - Hepatitis C Virus (HCV) co-infected patients. Some recent studies have found that cannabis use is negatively associated with insulin resistance in the general population and in HIV-HCV co-infected patients. Given the causal link between insulin resistance and steatosis, we hypothesized that cannabis use has a positive impact on steatosis. Therefore, we aimed to study whether cannabis use in this population was associated with a reduced risk of steatosis, measured by ultrasound examination. The ANRS CO13-HEPAVH cohort is a French nationwide multicenter of HIV-HCV co-infected patients. Medical and socio-behavioral data from clinical follow-up visits and annual self-administered questionnaires were prospectively collected. A cross-sectional analysis was conducted using data from the first visit where both ultrasound examination data for steatosis (positive or negative diagnosis) and data on cannabis use were available. A logistic regression model was used to evaluate the association between cannabis use and steatosis. Among study sample patients (n=838), 40.1% had steatosis. Fourteen percent reported daily cannabis use, 11.7% regular use, and 74.7% no use or occasional use (“never or sometimes”). Daily cannabis use was independently associated with a reduced prevalence of steatosis (adjusted odds ratio [95%]=0.64 [0.42;0.99]; p=0.046), after adjusting for body mass index, hazardous alcohol consumption and current or lifetime use of lamivudine/zidovudine. Daily cannabis use may be a protective factor against steatosis in HIV-HCV co-infected patients. These findings confirm the need for a clinical evaluation of cannabis-based pharmacotherapies in this population. Eudract.ema.europa.eu number, DGS050367. This article is protected by copyright. All rights reserved.

**Interferon-free therapy with direct acting antivirals for HCV/HIV-1 co-infected Japanese patients with inherited bleeding disorders.** Uemura H1,2, Tsukada K1, Mizushima D1, et al. PLoS One. 2017 Oct 18;12(10):e0186255. doi: 10.1371/journal.pone.0186255. eCollection 2017. INTRODUCTION: Almost 30 years ago, about 30% of Japanese hemophiliacs became infected with HIV-1 and hepatitis C virus (HCV) after receiving contaminated blood products. While several studies have reported the high efficacy and safety of direct acting antivirals (DAA) in HIV-1 co-infected patients, such data are limited in hemophiliacs. METHODS: We conducted a single-center, open-label study involving 27 Japanese patients (median age; 45 years) with inherited bleeding disorders who were co-infected with HCV/HIV-1. Patients with HCV genotype 1 (GT1) and GT4 received ledipasvir (90 mg) plus sofosbuvir (400 mg), those with HCV GT2 received sofosbuvir plus weight-based ribavirin, and those with HCV GT3 received daclatasvir (60 mg) plus sofosbuvir. Treatment was continued for 12 weeks in all patients. The primary endpoints were rate of sustained virologic response at 12 weeks after end of therapy (SVR12) and occurrence of adverse events during DAA therapy. RESULTS: Eighteen (67%) patients had had received interferon-based therapy, and 11 (41%) had compensated cirrhosis. HCV genotypes were GT1a 4 (15%), GT1b 16 (59%), GT1 undetermined 2 (7%), GT2a 1 (4%), GT3a 3 (11%) and GT4a 1 (4%). All patients were on combination antiretroviral therapy (cART) and had undetectable HIV-1 viral load (<20 copies/μL) at baseline. All patients achieved SVR12. Serious adverse events were observed in 3 patients: arteritis of the leg, which resolved after completion of DAA therapy, asymptomatic QT prolongation and gastrointestinal hemorrhage. cART failure was noted in one patient due to emergence of raltegravir resistance during ledipasvir/sofosbuvir treatment. Although α-fetoprotein, Mac-2 binding protein glycosylation isomer (M2BPGi), and Fibro Scan (FS) scores decreased in most patients during DAA therapy, M2BPGi (>2.0 cutoff index) and FS scores (>15.0 kPa) were still high in 6 patients at week 36.
CONCLUSIONS: DAA therapy is effective in all patients. However, adverse events and efficacy of cART should be monitored closely.


AIM: To evaluate the safety and efficacy of ledipasvir/sofosbuvir on hepatitis C eradication in patients with hepatitis C virus (HCV)/human immunodeficiency virus (HIV) co-infection in an urban HIV clinic. METHODS: A retrospective cohort study of 40 subjects co-infected with HIV-1 and HCV treated with the fixed-dose combination of ledipasvir and sofosbuvir for 12 wk from 2014 to 2016. All patients included were receiving antiretroviral therapy (ART) with HIV RNA values of 100 copies/mL or fewer regardless of baseline HCV RNA level. The primary end point was a sustained virologic response of HCV at 12 wk (SVR12) after the end of therapy.

RESULTS: Of the 40 patients enrolled, 55% were black, 22.5% had been previously treated for HCV, and 25% had cirrhosis. The patients were on a wide range of ART. Overall, 39 patients (97.5%) had a SVR 12 after the end of therapy, including rates of 97.1% in patients with HCV genotype 1a and 100% in those with HCV genotype 1b. One patient with HCV genotype 3a was included and achieved SVR12. Rates of SVR12 were similar regardless of previous treatment or the presence of compensated cirrhosis. Only 1 patient experienced relapse at week 12 following treatment and deep sequencing didn't reveal any resistance associated mutation in the NS5A or NS5B region. Interestingly, 7 (17.5%) patients who were adherent to ART experienced HIV viral breakthrough which resolved after continuing the same ART regimen. Two (5%) patients experienced HIV-1 virologic rebound due to noncompliance with HIV therapy, which resolved after resuming the same ART regimen. No severe adverse events were observed and no patient discontinued treatment because of adverse events. The most common adverse events included headache (12.5%), fatigue (10%), and diarrhea (2.5%). CONCLUSION: This retrospective study demonstrated the high rates of SVR12 of ledipasvir/sofosbuvir on HCV eradication in patients co-infected with HCV and HIV, regardless of HCV baseline levels, HCV treatment history or cirrhosis condition. The oral combination of ledipasvir/sofosbuvir represents a safe and well tolerated HCV treatment option that does not require modification for many of the common HIV ART. Occasional HIV virologic rebound occurred but later resolved without the need to change ART.


BACKGROUND: To describe the use of nonantiretroviral comedication and combination antiretroviral therapy (cART) in patients coinfected with HIV/hepatitis C virus (HCV) and to predict the potential for drug-drug interactions (DDIs) with direct-acting antivirals (DAAs) against HCV. METHODS: This is a retrospective, cross-sectional study, using the Dutch, nationwide ATHENA observational HIV cohort database. All patients with a known HIV/HCV coinfection on January 1, 2015, were included. Comedication and cART registered in the database were listed. The potential for DDIs between DAAs and comedication/cART were predicted using http://hep-druginteractions.org. DDIs were categorized as: (1) no clinically relevant DDI; (2) possible DDI; (3) contraindication; or (4) no information available.
RESULTS: We included 777 patients of whom 488 (63%) used nonantiretroviral comedication. At risk for a category 2/3 DDI with nonantiretroviral medications were 299 patients (38%). Most DDIs were predicted with paritaprevir/ritonavir, ombitasvir ± dasabuvir (47% of the drugs) and least with grazoprevir/elbasvir (11% of the drugs). Concerning cART, daclatasvir/sofosbuvir is the most favorable combination as no cART is contraindicated with this combination. In genotype 1/4 patients, grazoprevir/elbasvir is least favorable as 75% of the patients must alter their cART.

CONCLUSIONS: This study showed that comedication use in the aging HIV/HCV population is frequent and diverse. There is a high potential for DDIs between DAAs and comedication/cART.

Reproductive Aging and Hepatic Fibrosis Progression in Human Immunodeficiency Virus/Hepatitis C Virus-Coinfected Women.

BACKGROUND: Severity of hepatic fibrosis is greater in postmenopausal than in premenopausal women, perhaps owing to protective effects of estrogens. However, prior studies of estrogen and liver fibrosis lack serial fibrosis measures, adjustment for age, or longitudinal observations in coinfected populations.

METHODS: In a longitudinal cohort of women coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), we assessed fibrosis progression across reproductive age, using validated serum fibrosis markers, aminotransferase platelet ratio index (APRI) and fibrosis 4 (FIB-4). Fibrosis rate was evaluated within each woman as she transitioned from pre- to postmenopause, defined by a biomarker of ovarian function.

RESULTS: The median follow-up (n = 405) was 9.1 years (interquartile range, 5.0-15.2 years), with a median menopausal age of 49 years (47-52 years). When fully controlled for chronologic aging, the fibrosis progression rate was accelerated during perimenopause, as shown using FIB-4 (0.12 units per year faster than during premenopause; 95% confidence interval [CI], .02-.21; P = .01) and APRI (0.05 units per year faster; -.002 to .09; P = .06). Accelerated fibrosis was also observed during postmenopause compared with premenopause, for FIB-4 (0.14 units per year faster; 95% CI, .01 to .29; P = .07) and APRI (0.07 units per year faster; -.003 to .15; P = .06). Accelerated fibrosis in perimenopause persisted after adjustment for Hispanic ethnicity, antiretroviral use, and alcohol (0.10 FIB-4 units per year faster than during premenopause; 95% CI, .008-.20; P = .03). CONCLUSIONS: In HIV/HCV-coinfected women, hepatic fibrosis accelerates with reproductive aging. Accelerated fibrosis begins in perimenopause, highlighting a previously unrecognized group of women at increased risk for advanced fibrosis and associated complications. Longitudinal analyses of fibrosis rates across reproductive age should be conducted in non-HCV-related liver diseases, given potential implications in a broader spectrum of women.

The negative impact of HBV/HCV coinfection on cirrhosis and its consequences.

BACKGROUND: Hepatitis B virus (HBV)/hepatitis C virus (HCV) coinfection has been rarely studied in nonasian series. AIM: To compare the characteristics of HBV/HCV coinfected patients to those of HBV- or HCV-monoinfected patients in the ANRS CO22 HEPATHER cohort study. PATIENTS AND METHODS: Of the 20,936 included patients, 95 had HBV/HCV coinfection (hepatitis B surface antigen, anti-HCV antibody and HCV RNA positive)
and were matched with 375 HBV- and 380 HCV-monoinfected patients on age, gender and time since HBV or HCV diagnosis. RESULTS: F3-F4 fibrosis was more frequent in coinfected patients (58%) than in HBV- (32%, P < .0001), but similar in HCV-monoinfected patients (52%, P = .3142). Decompensated cirrhosis was more frequent in coinfected patients (11%) than in HBV- (2%, P = .0002) or HCV- (4%, P = .0275) monoinfected patients. Past excessive alcohol use was more frequent in coinfected patients (26%) than in HBV (12%, P = .0011), but similar in HCV monoinfected patients (32%, P = .2868). Coinfected patients had a higher proportion with arterial hypertension (42%) than HBV- (26%) or HCV-monoinfected patients (25%) (P < .003). Multivariable analysis confirmed the association between F3-F4 fibrosis and HCV infection in HBV-infected patients (OR = 3.84, 95% CI 1.99-7.43) and the association between decompensated cirrhosis and coinfection in HBV infected (OR = 5.58, 95% CI 1.42-22.0) or HCV infected patients (OR = 3.02, 95% CI 1.22-7.44). CONCLUSIONS: HCV coinfection harmfully affects liver fibrosis in HBV patients, while decompensated cirrhosis is increased in coinfected patients compared with HBV- or HCV-monoinfected patients. HCV treatment is as safe and effective in coinfected as monoinfected patients and should be considered following the same rules as HCV monoinfected patients.

COMPLEMENTARY AND ALTERNATIVE MEDICINE


Insight into the hepatoprotective effects of medicinally important plants is important, both for physicians and researchers. Main reasons for the use of herbal medicine include their lesser cost compared with conventional drugs, lesser undesirable drug reactions and thus high safety, and reduced side effects. The present review focuses on the composition, pharmacology, and results of experimental trials of selected medicinal plants: Silybum marianum (L.) Gaertn., Glycyrrhiza glabra, Phyllanthus amarus Schumach. & Thonn., Salvia miltiorrhiza Bunge., Astragalus membranaceus (Fisch.) Bunge, Capparis spinosa (L.), Cichorium intybus (L.), Solanum nigrum (L.), Sapindus mukorossi Gaertn., Ginkgo biloba (L.), Woodfordia fruticosa (L.) Kurz, Vitex trifolia (L.), Schisandra chinensis (Turcz.) Baill., Cuscuta chinensis (Lam.), Lycium barbarum, Angelica sinensis (Oliv.) Diels, and Litsea coreana (H. Lev.). The probable modes of action of these plants include immunomodulation, stimulation of hepatic DNA synthesis, simulation of superoxide dismutase and glutathione reductase to inhibit oxidation in hepatocytes, reduction of intracellular reactive oxygen species by enhancing levels of antioxidants, suppression of ethanol-induced lipid accumulation, inhibition of nucleic acid polymerases to downregulate viral mRNA transcription and translation, free radical scavenging and reduction of hepatic fibrosis by decreasing the levels of transforming growth factor beta-1, and collagen synthesis in hepatic cells. However, further research is needed to identify, characterize, and standardize the active ingredients, useful compounds, and their preparations for the treatment of liver diseases.

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EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Implementation of a multidisciplinary, team-based model to treat chronic hepatitis C in the primary care setting: Lessons learned. Sokol R1, Early J2, Barner A3, Gottfried S4, Gumpert
Hepatitis C virus (HCV) is the most common blood-borne virus in the U.S., and its incidence continues to rise. With approval of direct-acting antiviral medications, treatment for Chronic Hepatitis C (CHC) has become highly efficacious with a minimal side effect profile. Primary care physicians are well-positioned to address this increased demand, yet most do not feel comfortable treating CHC. In this case report, we describe implementation of a multidisciplinary team-based approach for treating CHC at multiple primary care sites across a large safety net health system. We focus on the evolving nature of implementation of our model through iterative Plan-Do-Study-Act (PDSA) cycles, highlighting the importance of developing an interdependent, multidisciplinary team, providing training, and ongoing support of Primary Care Hepatitis C Specialists, responding to the evolving nature of CHC treatment and policies, and ensuring high quality treatment. This process allowed us to continually grow and adapt our approach to make it feasible and successful. We share our "lessons" learned for others looking to bring CHC treatment, and potentially other specialty-based treatment, into the primary care setting.


BACKGROUND: Incarcerated populations are disproportionately burdened by hepatitis C virus (HCV) infection. The introduction of highly-effective, direct-acting antiviral (DAA) treatment has potential to substantially reduce the burden of liver disease in this population, but accurate information about access to and utilization of this treatment is currently limited. The goals of this study were to characterize receipt of HCV care and treatment services for a cohort of HCV-infected adults identified in a state prison system, and to describe the complex health needs of this population. METHODS: To estimate the proportion of patients who were treated for HCV while incarcerated, and the proportion linked to HCV care after release from prison, we used a deterministic matching algorithm to link administrative prison data, health care records, and a state public health surveillance database, which captures all positive HCV-related diagnostic test results through automatic laboratory reporting. Individuals not evaluated or treated for HCV while in prison were considered likely to have been linked to care in the community if the HCV surveillance system contained a record of a quantitative HCV RNA or genotype test within 6 months of their release date. Demographic and comorbidity data were manually extracted from the electronic health records for all patients referred for consideration of HCV treatment.

RESULTS: Between 2011 and 2015, 3126 individuals were known to be living with chronic HCV infection while incarcerated in the state prison system. Of these, 570 (18%) individuals were evaluated for HCV treatment while incarcerated and 328 (10%) initiated treatment with DAAs. Of the 2556 individuals not evaluated for treatment, 1605 (63%) were released from prison during the 5 year study period. Of these, 138 (9%) individuals engaged in HCV care in the community within 6 months. Data describing medical and psychiatric co-morbidities were available for the prison-based treatment cohort, which showed a high prevalence of major depression (39%), anxiety disorder (24%), alcohol misuse (52%), cocaine use (52%) and prior injection drug use (62%). CONCLUSION: Despite HCV treatment advances, linkage to care
and treatment rates for criminal-justice involved adults remains low, particularly for those who must seek care in the community after release from prison. Treating criminal-justice involved individuals for HCV during incarceration provides an opportunity to improve linkage to care and treatment rates among this vulnerable population.


State surveillance during the last 10 years reveals a nationwide increase in hepatitis C virus (HCV) infection among young adults (1). The proportion of infants born to HCV-infected women is also increasing nationally (2). To estimate the proportion of infants born to HCV-infected women and the frequency of confirmed HCV infection in their infants, maternal name and date of birth from HCV reports in the Wisconsin Electronic Disease Surveillance System (WEDSS) were linked to Wisconsin Medicaid data for 2011-2015 births. During this period, in the Wisconsin Medicaid population, the proportion of women who had evidence of HCV infection during pregnancy increased 93%, from 1 in 368 pregnancies to 1 in 192. Among 183 infants born to women with evidence of HCV viremia during pregnancy, 34% received recommended HCV testing (3). Mother-to-infant (vertical) transmission was documented in 4% of infants. Improvements in HCV screening practices among pregnant women and infants could enhance identification of infants at risk for vertical transmission of HCV.


AIMS: To evaluate hope in hepatitis C patients 9 years after curative treatment with pegylated interferon and ribavirin. BACKGROUND: Successful treatment of hepatitis C leads to improved quality of life in responders compared with non-responders. The long-term effect of successful treatment on hope in these patients is not known. DESIGN: Cross-sectional follow-up study of patients who displayed a sustained virological response to previous hepatitis C treatment. METHODS: Patients infected with hepatitis C genotype 2 or 3 from a randomized controlled study during 2004-2006 were included. A representative subgroup of those who achieved a sustained virological response was re-evaluated in 2012-2014. The patients were examined, had a blood test and completed a questionnaire (Herth Hope Index and demographic and clinical characteristics). The hope level was compared between patients and an age-matched sample from the general population (N = 1481). The data were analysed using multiple regression. RESULTS: A total of 104 Norwegian and Swedish hepatitis C patients were included in this follow-up study; their mean age was 48 years and 61% were men. Patients treated for hepatitis C scored higher than the general population on the total Herth Hope Index and for 11 of the 12 individual items. Age, gender, educational level, employment status and civil status were associated with a higher Herth Hope Index in those who had received hepatitis C treatment. CONCLUSION: Patients achieving a sustained viral response had a higher hope level than the general population 9 years after successful treatment of hepatitis C virus infection.

**Increasing Prevalence of Hepatitis C among Hospitalized Children Is Associated with an Increase in Substance Abuse.** Barritt AS 4th1, Lee B2, Runge T1, Schmidt M3, Jhaveri R4. J
OBJECTIVE: To evaluate the impact of substance abuse on pediatric hepatitis C virus (HCV) prevalence, we examined geographic and demographic data on inpatient hospitalizations in children with HCV. STUDY DESIGN: We examined hospitalizations in children using the Kids' Inpatient Database, a part of the Healthcare Cost and Utilization Project. We identified cases using the International Classification of Diseases, 9th edition, codes for HCV infection during 2006, 2009, and 2012. Nonparametric tests for trend were used to calculate trend statistics. RESULTS: From 2006 to 2012 nationally, the number of hospitalizations of children with HCV increased 37% (2.69 to 3.69 per 10 000 admissions; P < .001). The mean age of children hospitalized was 17.6 years (95% CI, 17.4-17.8). HCV cases among those 19-20 years of age represented 68% of the total HCV diagnoses, with a 54% increase over the years sampled (P < .001 for trend). The burden of HCV in children was highest in whites, those in the lowest income quartile, and in the Northeast and Southern regions of the US (all P < .0001). The prevalence of substance use among children with HCV increased from 25% in 2006 to 41% in 2012 (P < .001). CONCLUSION: The increases of HCV in hospitalized children are largely in teenagers, highly associated with substance abuse, and concentrated in Northeast and Southern states. These results strongly suggest that public health efforts to prevent and treat HCV will also need to include adolescents.


PURPOSE: Examine the prevalence of hepatitis C virus (HCV) screening, confirmatory testing, and care experiences among young adult nonmedical prescription opioid (NMPO) users.

METHODS: We examined self-reported HCV screening history in a sample of 18- to 29-year-olds reporting past-month NMPO use, and we used modified Poisson regression to identify associated sociodemographic and drug use patterns. RESULTS: Among 196 participants, 154 (78.6%) reported prior HCV screening, among whom 18 (11.7%) reported positive results. Of these, 13 (72.2%) reported receiving a confirmatory test; 12 (66.7%) were referred for specialty HCV care. Screening was associated with injection drug use (adjusted prevalence ratio [APR] = 1.19; 95% confidence interval [CI] = 1.05-1.33) and history of hospitalization for psychiatric illness (APR = 1.23; 95% CI = 1.09-1.39). Younger participants (18-23 years) were less likely to have been screened (APR = .69; 95% CI = .57-.85). CONCLUSION: Among young adult NMPO users, post-HCV screening support and referral to care were inadequate.

Should we treat acute hepatitis C? A decision and cost-effectiveness analysis. Bethea E1,2,3, Chen Q1,2, Hur C1,2,3, Chung RT2,3, Chhatwal J1,2,3. Hepatology. 2017 Oct 23. doi: 10.1002/hep.29611. [Epub ahead of print]

It is not standard practice to treat patients with acute hepatitis C virus (HCV) infection. However, as the incidence of HCV in the United States continues to rise, it may be time to re-evaluate acute HCV management in the era of direct-acting antiviral agents (DAAs). In this study a microsimulation model was developed to analyze the tradeoffs between initiating HCV therapy in the acute versus chronic phase of infection. By simulating the lifetime clinical course of patients with acute HCV infection, we were able to project long-term outcomes such as quality-adjusted life years (QALYs) and costs. We found that treating acute HCV versus deferring treatment until the chronic phase increased QALYs by 0.02 and increased costs by $483 in
The resulting incremental cost effectiveness ratio (ICER) was $19,991 per QALY, demonstrating that treatment of acute HCV was cost-effective using a willingness-to-pay threshold of $100,000 per QALY. In patients at risk of transmitting HCV, treating acute HCV became cost-saving, increasing QALYs by 0.03 and decreasing costs by $3655. **CONCLUSION:** Immediate treatment of acute HCV with DAAs can improve clinical outcomes and be highly cost-effective or cost-saving compared with deferring treatment until the chronic phase of infection. If future studies continue to demonstrate effective HCV cure with shorter 6 week treatment duration, then it may be time to revisit current HCV guidelines to incorporate recommendations that account for the clinical and economic benefits of treating acute HCV in the era of DAAs. This article is protected by copyright. All rights reserved. © 2017 by the American Association for the Study of Liver Diseases.


**BACKGROUND:** High prices of direct acting antivirals (DAAs) for hepatitis C virus (HCV) can lead to restrictions on access to treatment in high- and middle-income countries. An increasing number of people in these countries are treating their HCV infection with generic drugs produced in India, China, Bangladesh or Egypt. This analysis assessed the efficacy of generic imported DAAs. **METHODS:** Patients sourced generic versions of sofosbuvir (SOF), ledipasvir (LDV) and daclatasvir (DCV) from suppliers in India, Bangladesh, China and Egypt via three buyers' clubs. The choice of DAAs and the length of treatment were determined on baseline RNA levels, HCV genotype and stage of fibrosis. Patient HCV RNA levels were evaluated pre-treatment, during treatment, at end of treatment (EOT) and then for sustained virological response (SVR) at 4, 12, and 24 weeks, normally by a treating clinician. **RESULTS:** Overall 616 patients submitted results: 199 from an Australian buyers' club, 205 from a South-east Asian buyers' clubs, and 212 from an Eastern European buyers' club. Of the 616 patients treated, 276 received SOF/LDV (35 with ribavirin [RBV]) and 340 received SOF/DCV (61 with RBV). At baseline, 61% were male, 52% had HCV genotype 1 and 11% had liver cirrhosis. The mean age was 44.3 years and the mean baseline HCV RNA was 6.9 log10 IU/mL. A rapid virological response (RVR) was observed in 314/375 (84%) of the patients treated. Based on currently available data, the percentage of patients with HCV RNA below the lower limit of quantification (LLOQ) was 99% (234/237) at EOT, 99% (299/303) at SVR4 and 99% (247/250) at SVR12. **CONCLUSIONS:** In this analysis, treatment with imported generic DAAs achieved high rates of HCV RNA undetectability at the end of treatment, and SVR12 in 99% of patients evaluated to date. Mass treatment with generic DAAs is a feasible and economical alternative route of accessing curative DAAs, where the high prices for branded alternatives prevent access to treatment.


On July 18, 2017, the US Food and Drug Administration (FDA) approved sofosbuvir/ velpatasvir/voxilaprevir (SOF/VEL/VOX) (Vosevi) fixed-dose combination (FDC), an interferon-free, complete regimen for adult patients with chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have: genotype 1,
2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor; and genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor. Approval was based on an acceptable safety profile and high sustained virologic response rates 12 weeks after the end-of-treatment (SVR12) in two phase 3 clinical trials in subjects previously treated with a direct-acting antiviral (DAA) regimen. In POLARIS-1, 96% of SOF/VEL/VOX treated subjects achieved SVR12. In POLARIS-4, 98% of SOF/VEL/VOX treated subjects achieved SVR12. A key and challenging question in evaluating the data was determining the contribution of VOX to SOF/VEL and how this differed depending on the genotype and patient population. In this article, we provide our perspective on the issues considered in making these determinations, especially regarding the POLARIS-4 data in subjects who have previously been treated with a chronic HCV regimen containing sofosbuvir (SOF) without an NS5A inhibitor. CONCLUSION: We seek to provide context as to why a broad indication was given for NS5A inhibitor-experienced patients (HCV genotypes 1-6) while the indication for NS5A inhibitor-naïve patients was limited to HCV genotypes 1a and 3 only. This article is protected by copyright. All rights reserved.

Demographics, Resource Utilization, and Outcomes of Elderly Patients With Chronic Liver Disease Receiving Hospice Care in the United States. Fukui N1, Golabi P2, Otgonsuren M2, Mishra A1,2, Venkatesan C1, Younossi ZM1,2. Am J Gastroenterol. 2017 Nov;112(11):1700-1708. doi: 10.1038/ajg.2017.290. Epub 2017 Oct 10. OBJECTIVES: Hospice offers non-curative symptomatic management to improve patients' quality of life, satisfaction, and resource utilization. Hospice enrollment among patients with chronic liver disease (CLD) is not well studied. The aim of this study is to examine the characteristics of Medicare enrollees with CLD, who were discharged to hospice. METHODS: Medicare patients discharged to hospice between 2010 and 2014 were identified in Medicare Inpatient and Hospice Files. CLDs and other co-morbidities were identified by International Classification of Diseases-ninth revision codes. Generalized linear model was used to estimate regression coefficients with P-values. Logistic regression was used to calculate odds ratios and 95% confidence intervals. RESULTS: A total of 2,179 CLD patients and 34,986 controls without CLD met the inclusion criteria. Non-alcoholic fatty liver disease, alcoholic liver disease, and hepatitis C virus (HCV) were the most frequent cause of CLD. CLD patients were younger (70 vs. 83 years), more likely to be male (57.7 vs. 39.3%), had longer hospital stay (length of stay, LOS) (19.4 vs. 13.0 days), higher annual charges ($175,000 vs. $109,000), higher 30-day re-hospitalization rates (51.6 vs. 34.2%), and shorter hospice LOS (13.7 vs. 17.7 days) than controls (all P<0.001). Presence of HCV and congestive heart failure were the strongest contributors to increased total annual costs (34% and 31% higher, P<0.001), increased total annual LOS (26% and 43% higher, P<0.001), and increased 30-day readmission risk (2.20 and 2.19 times, respectively). CONCLUSIONS: Patients with CLD have longer and costly hospitalizations before hospice enrollment as compared with patients without CLD. It was highly likely that these patients were enrolled relatively late, which could potentially lead to less benefit from hospice.

Hepatocellular (Liver) Cancer

Association between PNPLA3 (rs738409 C>G) variant and hepatocellular carcinoma in Asian chronic hepatitis C patients: A longitudinal study. Yen YH1, Tsai MC1, Wu CK1, et
BACKGROUND/PURPOSE: Previous meta-analyses assess whether or not patatin-like phospholipase domain containing 3 (PNPLA3) (rs738409 C > G) was associated with increased risk of hepatocellular carcinoma (HCC) in Caucasians patients with hepatitis C virus (HCV)-related cirrhosis, these meta-analyses did not provide firm conclusions. Only one cross-sectional study involving Asian patients has previously been conducted to explore this issue. We aim to investigate this in a longitudinal cohort of Asian chronic hepatitis C (CHC) patients.

METHODS: We consecutively enrolled 1011 CHC patients who underwent liver biopsy before initiating interferon-based therapy. These patients were followed-up and screened for HCC up to a median of 6.9 years. The influence of rs738409 (GG) genotype on the occurrence of HCC was assessed using the Kaplan-Meier method, then according to the multivariate Cox model.

RESULTS: During follow-up, 143 (14.1%) patients developed HCC. rs738409 (GG) genotype was not associated with time-to-HCC development on multivariate Cox regression (P = 0.634). When considering the occurrence of these events over time, rs738409 (GG) genotype did not influence the risk of HCC development (log-rank = 0.12). Among 261 patients with liver cirrhosis, rs738409 (GG) genotype was not associated with time-to-HCC development on multivariate Cox regression (P = 0.737). When considering the occurrence of these events over time, rs738409 (GG) genotype did not influence the risk of HCC development (log-rank = 0.72).

CONCLUSION: In this longitudinal study with liver biopsy to stage liver fibrosis, we affirm there is no influence of the rs738409 (GG) genotype on the occurrence of HCC in Asian CHC patients, including cirrhotic patients.


AIM: To investigate gender-specific liver estrogen receptor (ER) expression in normal subjects and patients with hepatitis C virus (HCV)-related cirrhosis and hepatocellular carcinoma (HCC).

METHODS: Liver tissues from normal donors and patients diagnosed with HCV-related cirrhosis and HCV-related HCC were obtained from the NIH Liver Tissue and Cell Distribution System. The expression of ER subtypes, ERα and ERβ, were evaluated by Western blotting and real-time RT-PCR. The subcellular distribution of ERα and ERβ was further determined in nuclear and cytoplasmic tissue lysates along with the expression of inflammatory [activated NF-kB and IκB-kinase (IKK)] and oncogenic (cyclin D1) markers by Western blotting and immunohistochemistry. The expression of ERα and ERβ was correlated with the expression of activated NF-kB, activated IKK and cyclin D1 by Spearman's correlation.

RESULTS: Both ER subtypes were expressed in normal livers but male livers showed significantly higher expression of ERα than females (P < 0.05). We observed significantly higher mRNA expression of ERα in HCV-related HCC liver tissues as compared to normals (P < 0.05) and ERβ in livers of HCV-related cirrhosis and HCV-related HCC subjects (P < 0.05). At the protein level, there was a significantly higher expression of nuclear ERα in livers of HCV-related HCC patients and nuclear ERβ in HCV-related cirrhosis patients as compared to normals (P < 0.05). Furthermore, we observed a significantly higher expression of phosphorylated NF-kB and cyclin D1 in diseased livers (P < 0.05). There was a positive correlation between the expression of nuclear ER subtypes and nuclear cyclin D1 and a negative correlation between cytoplasmic ER subtypes and cytoplasmic phosphorylated IKK in HCV-related HCC livers. These findings suggest that
dysregulated expression of ER subtypes following chronic HCV-infection may contribute to the progression of HCV-related cirrhosis to HCV-related HCC. CONCLUSION: Gender differences were observed in ERα expression in normal livers. Alterations in ER subtype expression observed in diseased livers may influence gender-related disparity in HCV-related pathogenesis.


Hepatitis C virus (HCV) infection is a major risk factor for the development of chronic liver disease. The disease typically progresses from chronic HCV to fibrosis, cirrhosis, hepatocellular carcinoma (HCC), and death. Chronic inflammation associated with HCV infection is implicated in cirrhosis and HCC, but the molecular players and signaling pathways contributing to these processes remain largely unknown. Interferon regulatory factor 5 (IRF5) is a molecule of interest in HCV-associated HCC because it has critical roles in virus-, Toll-like receptor (TLR)-, and interferon (IFN)-induced signaling pathways. IRF5 is also a tumor suppressor, and its expression is dysregulated in several human cancers. Here, we present first evidence that IRF5 expression and signaling are modulated during HCV infection. Using HCV infection of human hepatocytes and cells with autonomously replicating HCV RNA, we found that levels of IRF5 mRNA and protein expression were downregulated. Of note, reporter assays indicated that IRF5 re-expression inhibited HCV protein translation and RNA replication. Gene expression analysis revealed significant differences in the expression of cancer pathway mediators and autophagy proteins rather than in cytokines between IRF5- and empty vector-transfected HCV replicon cells. IRF5 reexpression induced apoptosis via loss in mitochondrial membrane potential, downregulated autophagy, and inhibited hepatocyte cell migration/invasion. Analysis of clinical HCC specimens support a pathologic role for IRF5 in HCV-induced HCC, as IRF5 expression was down-regulated in livers from HCV-positive versus HCV-negative HCC patients or healthy donor livers. These results identify IRF5 as an important suppressor of HCV replication and HCC pathogenesis.


BACKGROUND: With the development of direct-acting anti-virals (DAAs), almost all patients with chronic hepatitis C virus (HCV) infection can achieve sustained viral response (SVR).

AIM: To evaluate the short-term risk of HCC among patients with SVR by DAAs, including those with cirrhosis or previous HCC.

METHODS: This large-scale, multicentre cohort study included 1,675 consecutive patients who achieved SVR by treatment with interferon-free sofosbuvir-based regimens, divided into groups with (n = 152) or without previous HCC (n = 1,523). The Kaplan-Meier method and Cox proportional hazard analysis were used to calculate the cumulative HCC incidence and related factors of HCC.

RESULTS: During the follow-up period (median: 17 months), 46 (2.7%) patients developed HCC. The 1-year cumulative rates of de novo HCC were 0.4% and 4.9% for the noncirrhosis and cirrhosis groups respectively (log-rank test: P < 0.001). For cirrhotic patients, serum α-fetoprotein level at the end of treatment (EOT-AFP) was the strongest predictor of de novo HCC. The 1-year cumulative de novo HCC...
rates were 1.4% and 13.1% in the EOT-AFP < 9.0 ng/mL and ≥ 9.0 ng/mL groups (cut-off value) respectively (log-rank test: P < 0.001). The 1-year cumulative rates of HCC recurrence were 6.5% and 23.1% for the noncirrhosis and cirrhosis groups respectively (log-rank test: P = 0.023). For cirrhotic patients, previous HCC characteristics were significantly associated with HCC recurrence. In contrast, sex, age and metabolic features did not influence de novo HCC or recurrence. **CONCLUSIONS:** For cirrhotic patients after elimination of HCV, serum EOT-AFP level and previous HCC characteristics would be useful markers for predicting de novo HCC or recurrence.


**BACKGROUND:** The achievement of high rates of sustained virological response (SVR) with direct-acting antivirals (DAAs) in hepatitis C virus (HCV) infected patients will reduce decompensating terminal events. **AIMS:** To investigate whether hepatocellular carcinoma (HCC) occurrence could change due to the DAA-induced increase in life-expectancy. **METHODS:** A Markov model was built on clinical data of 494 cirrhotic patients and available literature to estimate probabilities of "death before HCC" and of "HCC occurrence" without and with DAA. **RESULTS:** In comparison to untreated patients, DAA therapy reduced the 20-year mortality before HCC by 21.9% in patients without varices and by 21.5% in those with varices, considering an SVR of 95% and no direct effect on hepatocarcinogenesis. Tumour occurrence increased by 5%-8.2% and the proportion of HCCs diagnosed in compensated stages increased to >98%. If we consider DAA as having "anti-tumoral" effects, the benefit becomes greater, achieving a 20-year survival of 81.5% in patients without varices, and 52.2% in patients with varices. Instead, if we consider DAA as having a "pro-tumoral" effect, then, the increased incidence of HCC nullifies the survival benefits. **CONCLUSION:** DAAs drastically reduce the mortality caused by the liver function worsening, increasing the proportion of HCCs diagnosed in compensated stages. Knowledge of the DAA effect on hepatocarcinogenesis remains pivotal.


**BACKGROUND & AIMS:** Although hepatitis B virus (HBV) and hepatitis C virus (HCV) infections remain major risk factors for hepatocellular carcinoma (HCC), non-viral causes of HCC, particularly non-alcoholic fatty liver disease (NAFLD), are becoming increasingly prevalent. The aim of this study was to compare the clinical characteristics and survival of cryptogenic and viral HCC. **METHODS:** We conducted a retrospective cohort study involving 3878 consecutive HCC patients seen at two tertiary centres in the United States and one in Taiwan from 2004 to 2014. We compared the clinical characteristics, treatment and survival of patients by underlying aetiology: cryptogenic (n = 696), HBV (n = 1304) or HCV (n = 1878). **RESULTS:** Cirrhosis was present in 66.8% of the cryptogenic HCC patients, compared with 74.7% of HBV-related HCC (HBV-HCC) (P = .001) and 85.9% of HCV-HCC (P < .001). Compared to viral HCC, cryptogenic HCC patients presented with larger tumours and at later stages of disease. Five-year overall survival was 16.3% among cryptogenic HCC patients compared with 31.9% among HBV-HCC patients and 27.7% among HCV-HCC patients (P <
CONCLUSIONS: Compared with viral HCC patients, those with cryptogenic HCC had lower prevalence of cirrhosis, were diagnosed with larger tumours at more advanced stages of disease, and had poorer overall survival. Additional efforts are needed to identify patients at risk of cryptogenic HCC and to identify cryptogenic HCC at earlier stages of disease.


Tumor necrosis factor related apoptosis-inducing ligand (TRAIL) plays an important role in many cancers including hepatocellular carcinoma (HCC). The aim of this study is to investigate the association of the DR4 polymorphisms C626G (Thr209Arg, rs20575) and A683C (Glu228Ala, rs20576) with the occurrence of HCC in Egyptian patients chronically infected with HCV. The study included 80 patients with HCV-related HCC (group 1) and 80 patients with HCV-related liver cirrhosis (group 2) who are naïve to treatment. Clinical and laboratory data were recorded. Genotyping of TRAIL receptor DR4 polymorphism C626G rs20575 and A683C rs20576 SNP was done by Real-Time PCR using taqman probes technology. The mean age of HCC patients was 57.6 ± 8.4 years with 62 patients (77.5%) were males. While group 2 mean age was 49.5 ± 10.29 years with 50% were males. The frequency distribution of rs20575 genotypes showed a statistically significant difference between the two studied groups (P = 0.02), the carriers of the C allele were 2.01 times more likely to develop HCC than the carriers of the G allele (P = 0.003), while no significant difference in rs20576 genotypes distribution was found between the studied groups (P = 0.680). On combining the carriers of C allele of rs20575 and the carriers of A allele of rs20576, a significant difference was detected (P > 0.001) with 2.85 higher risk of HCC development in patients who carried both genetic risk alleles simultaneously. The significant difference in DR4 polymorphisms among HCC and cirrhotic patients suggests their role as potential risk factors of HCC development.


Most mortalities from liver disease and liver cancer worldwide are attributable to hepatitis B virus (HBV) and hepatitis C virus. Despite remarkable advances in the treatment of HBV over past decades, limited population-level data are available regarding its impact on burden of liver disease and liver cancer. Mortality data from liver disease and liver cancer were obtained from the national death certificate database of Korea, an HBV-endemic country, between 1999 and 2013, and were analyzed by Joinpoint analysis. For liver disease, number of annual deaths decreased by 62.3% (95% confidence interval [CI], 62.0-62.6), crude death rate (CDR) decreased by 64.6% (95% CI, 64.3-64.9) from 21.2 to 7.5 per 100,000 population, and age-standardized death rate (ADR) declined by 75.0% (95% CI, 74.7-75.3), between 1999 and 2013. In contrast, for liver cancer, number of annual deaths increased by 17.8% (95% CI, 17.6-18.0) and CDR increased by 10.2% (95% CI, 10.0-10.4) from 20.5 to 22.6, although ADR decreased by 26.9% (95% CI, 26.6-27.2). The annual number of patients receiving oral antiviral agents against HBV increased from 1,716 to 187,226 during the study period. The increase in mean age
at death from liver disease was significantly greater than that from liver cancer (8.8 vs. 6.1 years: P = 0.02). **CONCLUSION:** Marked reduction in liver disease mortality by widespread use of antiviral treatments against HBV may increase the life expectancy and number of patients at risk of developing liver cancer, inadvertently leading to increased burden of liver cancer in an HBV-endemic population. The competing nature between death from liver disease and that from liver cancer should be carefully considered in establishing a health care policy.

**Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine.**
Chronic fibrotic liver disease caused by viral or metabolic etiologies is a high-risk condition for developing hepatocellular carcinoma (HCC). Even after complete HCC tumor resection or ablation, the carcinogenic tissue microenvironment in the remnant liver can give rise to recurrent de novo HCC tumors, which progress into incurable, advanced-stage disease in the majority of patients. Thus, early detection and prevention of HCC development is, in principle, the most impactful strategy to improve patient prognosis. However, practice guideline-recommended "one-size-fits-all" HCC screening for early tumor detection is utilized in less than 20% of the target population, and performance of screening modalities, i.e., ultrasound and alpha-fetoprotein is suboptimal. Furthermore, optimal screening strategies for emerging at-risk patient populations such as chronic hepatitis C after viral cure and non-cirrhotic non-alcoholic fatty liver disease remain controversial. New HCC biomarkers and imaging modalities may improve sensitivity and specificity of HCC detection. Clinical and molecular HCC risk scores will enable precise HCC risk prediction followed by tailored HCC screening for individual patients to maximize its cost-effectiveness and optimize allocation of limited medical resources. Several etiology-specific and generic HCC chemoprevention strategies are evolving. Epidemiological and experimental studies have identified candidate chemoprevention targets and therapies, including statins, anti-diabetic drugs, and selective molecular targeted agents, although their clinical testing has been limited by the lengthy process of cancer development that requires long-term, costly studies. Individual HCC risk prediction is expected to overcome the challenge by enabling personalized chemoprevention targeting high-risk patients to achieve precision HCC prevention and substantially improve the dismal prognosis of HCC.