
BACKGROUND: The aim of the study was to investigate whether patients with a previous nonresponse to standard of care treatment with ribavirin dosed according to body weight would respond to a high individualized dose of concentration-monitored ribavirin. METHODS: Previous nonresponders to standard of care treatment with peginterferon (peg-IFN) and ribavirin were included. Ribavirin was dosed aiming at a plasma concentration of >15 μmol/L. The initial ribavirin dose was calculated from a formula based on renal function and body weight. Erythropoietin treatment was started 2 weeks before antiviral therapy. RESULTS: Twenty patients (16 men and 4 women) with a mean age of 52 years were included. Sixty percent had advanced fibrosis. Eighty percent of patients achieved an early viral response, and 60% were negative for hepatitis C virus ribonucleic acid (HCV RNA) at treatment week 24. High-dose ribavirin resulted in a significantly increased HCV RNA drop at week 12 (mean: 3.13 versus 2.05 IU/mL; P < 0.001). Nine patients were negative for HCV RNA at the end of treatment, and 1 achieved sustained viral response. The final steady-state daily dose of ribavirin varied from 1400 to 4400 mg. Hemoglobin levels decreased during treatment, mean Hb 163, 134, and 110 g/L at week 0, 4, and 12, respectively. Two patients received blood transfusions. No other severe adverse events were recorded. CONCLUSIONS: An individualized high ribavirin dose resulted in a more pronounced early viral HCV RNA decline than a standard-dose ribavirin scheme. This regime is safe provided that close monitoring of anemia is undertaken and that treatment with erythropoietin is given.


BACKGROUND & AIMS: We compared outcomes by cirrhosis status across studies of the all-oral combination of daclatasvir (DCV) plus asunaprevir (ASV). METHODS: Outcomes from global and Japanese phase 2 and 3 clinical studies of DCV+ASV in patients with genotype (GT) 1b infection were assessed by cirrhosis status. Sustained virological response (SVR) was assessed in individual phase 3 studies; a pooled analysis was carried out for safety outcomes.
RESULTS: In the Japanese phase 3 study, SVR12 was achieved by 91% of patients with cirrhosis (n=22) and 84% of patients without cirrhosis (n=200); in the global phase 3 study SVR12 was achieved by 84% of patients with cirrhosis (n=206) and by 85% of patients without cirrhosis (n=437). The frequency of serious adverse events, adverse events leading to treatment discontinuation, and treatment-emergent grade 3/4 lab abnormalities was low (<10%), and similar among patients with (n=229) or without (n=689) compensated cirrhosis receiving DCV+ASV. Grade 3/4 reductions in platelets and neutrophils were more common among patients with cirrhosis (1.3% and 2.2%, respectively) than in those without cirrhosis (both 0.6%). Grade 3/4 liver function test abnormalities were less common among patients with cirrhosis (1.8%) than in those without cirrhosis (3.5%-4.7%). Alanine aminotransferase elevations were not associated with hepatic decompensation. CONCLUSIONS: The safety and efficacy of DCV+ASV were similar in patients with or without compensated cirrhosis. This all-oral, interferon- and ribavirin-free combination is an effective and well tolerated treatment option for patients with HCV GT1b infection and cirrhosis.

Given the associated risk of PD with HCV, what are some innovative initiatives to harness the support of another disease-specific group, like Parkinson Disease, to further increase awareness of HCV?

Hepatitis C virus infection as a risk factor for Parkinson disease: A nationwide cohort study. Tsai HH1, Liou HH1, Muo CH1, Lee CZ1, Yen RF1, Kao CH2. Neurology. 2015 Dec 23. pii: 10.1212/WNL.0000000000002307. [Epub ahead of print]

OBJECTIVE: To determine whether hepatitis C virus (HCV) infection is a risk factor for developing Parkinson disease (PD).

METHODS: This nationwide population-based cohort study was based on data obtained from a dataset of the Taiwan National Health Insurance Research Database for the period 2000 to 2010. A total of 49,967 patients with viral hepatitis were included for analysis. Furthermore, 199,868 people without viral hepatitis were included for comparisons. Patients with viral hepatitis were further grouped into 3 cohorts: hepatitis B virus (HBV) infection, HCV infection, and HBV-HCV coinfection. In each cohort, we calculated the incidence of developing PD. A Cox proportional hazards model was applied to estimate the risk of developing PD in terms of hazard ratios (HRs) and 95% confidence intervals (CIs).

RESULTS: The crude HRs for developing PD was 0.66 (95% CI = 0.55-0.80) for HBV infection, 2.50 (95% CI = 2.07-3.02) for HCV infection, and 1.28 (95% CI = 0.88-1.85) for HBV-HCV coinfection. The association between HCV and PD remained statistically significant after adjustments for age, sex, and comorbidities (adjusted HR = 1.29, 95% CI = 1.06-1.56).

CONCLUSIONS: We conducted a large nationwide population-based study and found that patients with HCV exhibit a significantly increased risk of developing PD.


BACKGROUND: The role of inflammation in mood disorders has received increased attention. There is substantial evidence that cytokine therapies, such as interferon alpha (IFN-alpha), can induce depressive symptoms. Indeed, proinflammatory cytokines change brain function in several ways, such as altering neurotransmitters, the glucocorticoid axis, and apoptotic mechanisms. This study aimed to evaluate the impact on mood of initiating IFN-alpha and...
ribavirin treatment in a cohort of patients with chronic hepatitis C. We investigated clinical, personality and functional genetic variants associated to cytokine-induced depression.

**METHODS:** We recruited 344 Caucasian outpatients with chronic hepatitis C initiating IFN-alpha and ribavirin therapy. All patients were euthymic at baseline according to DSM-IV-R criteria. Patients were assessed at baseline, 4, 12, 24, and 48 weeks after treatment initiation using the Patient Health Questionnaire (PHQ) and the Hospital Anxiety and Depression Scale (HADS) and the Temperament and Character Inventory (TCI). We genotyped several functional polymorphisms of interleukin-28 (IL28B), indoleamine 2,3-dioxigenase (IDO-1), serotonin receptor-1A (HTR1A), catechol-O-methyl transferase (COMT), glucocorticoid receptors (GCR1 and GCR2), brain-derived neurotrophic factor (BDNF) and FK506 binding protein 5 (FKBP5) genes. A survival analysis was performed, and the Cox proportional hazards model was used for the multivariate analysis.

**RESULTS:** The cumulative incidence of depression was 0.35 at week 24 and 0.46 at week 48. The genotypic distributions were in Hardy-Weinberg equilibrium. Older age (p=0.018, hazard ratio per 5 years=1.21), presence of depression history (p=0.0001, HR=2.38), and subthreshold depressive symptoms at baseline (p=0.005, HR=1.13) increased the risk of IFN-induced depression. So too did TCI-personality traits, with high scores on fatigability (p=0.0037, HR=1.17), impulsiveness (p=0.0200 HR= 1.14), disorderliness (p=0.0339, HR=1.11), and low scores on extravagance (p=0.0040, HR=0.85). An interaction between HTR1A and COMT genes was found. Patients carrying the G allele of HTR1A plus the Met substitution of the COMT polymorphism had a greater risk for depression during antiviral treatment (HR=3.83) than patients with the CC (HTR1A) and Met allele (COMT) genotypes. Patients carrying the HTR1A CC genotype and the COMT Val/Val genotype (HR=3.25) had a higher risk of depression than patients with the G allele (HTR1A) and the Val/Val genotype. Moreover, functional variants of the GCR1 (GG genotype: p= 0.0436, HR=1.88) and BDNF genes (Val/Val genotype: p=0.0453, HR=0.55) were associated with depression.

**CONCLUSIONS:** The results of the study support that IFN-induced depression is associated with a complex pathophysiological background, including serotonergic and dopaminergic neurotransmission as well as glucocorticoid and neurotrophic factors. These findings may help to improve the management of patients on antiviral treatment and broaden our understanding of the pathogenesis of mood disorders.

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**Pharmacokinetics and tolerability of paritaprevir, a direct-acting antiviral agent for HCV treatment, with and without ritonavir in healthy volunteers.**


**AIMS:** Paritaprevir is a direct-acting antiviral agent for use as part of multidrug hepatitis C virus infection treatment regimen. To characterize the pharmacokinetics, safety, and tolerability of paritaprevir and determine an optimal dosing regimen for subsequent evaluations, clinical studies were conducted with paritaprevir alone or with ritonavir, a cytochrome P450 3A4 inhibitor anticipated to increase paritaprevir exposure.

**METHODS:** Two phase 1, double-blind, placebo-controlled, parallel-group studies were conducted in healthy volunteers (NCT00850044 and NCT00931281). Single-dose study participants (N = 87) were randomized to one-time administration of either paritaprevir or placebo, or paritaprevir with ritonavir or placebo. Participants (N = 38) enrolled in the multiple-dose study received paritaprevir with ritonavir or placebo once or twice daily for 14 days. Pharmacokinetics, safety, and tolerability were assessed throughout the study treatment periods.

**RESULTS:** After single- or multiple-dose
administration, paritaprevir displayed non-linear pharmacokinetics, with maximum plasma concentration and area under the plasma concentration-time curve increasing in a greater than dose-proportional manner. Concomitant administration of 100 mg ritonavir increased paritaprevir exposure from a 300-mg dose approximately 30- to 50-fold and extended paritaprevir half-life. The tolerability of paritaprevir was similar with or without ritonavir. Asymptomatic, transient increases in bilirubin were observed but were not associated with abnormalities in other liver function tests. **CONCLUSIONS:** Paritaprevir exhibits non-linear pharmacokinetics with greater-than-dose-proportional increases in exposure after single or multiple dosing. Co-administration with ritonavir increases paritaprevir exposure and half-life without adversely influencing tolerability.


**BACKGROUND:** ABT-493 is a hepatitis C virus (HCV) non-structural (NS) protein 3/4A protease inhibitor, and ABT-530 is an HCV NS5A inhibitor. These direct-acting antivirals (DAAs) demonstrated potent antiviral activity against major HCV genotypes and high barriers to resistance in vitro. **METHODS:** In this open-label dose-ranging trial, antiviral activity and safety were assessed during 3 days of monotherapy with ABT-493 or ABT-530 in treatment-naïve adults with HCV genotype 1 infection, with/without compensated cirrhosis. Presence of baseline resistance-associated variants (RAVs) and safety were also evaluated. **RESULTS:** Mean maximal decreases from baseline in HCV RNA were approximately 4 log10 IU/mL for all ABT-493 doses ranging from 100 mg - 700 mg and doses ≥40 mg for ABT-530. There was no meaningful difference in viral load decline in patients with or without compensated cirrhosis. Twenty-four (50%) of the baseline samples from patients treated with ABT-493 had RAVs to NS3/4A protease inhibitors. Among 40 patients treated with ABT-530, 6 (15%) carried baseline RAVs to NS5A inhibitors. Viral load declines in patients with single baseline NS5A RAVs were similar to those in patients without them. One patient harbored baseline RAVs at 3 NS5A positions and appeared to have slightly less robust viral load decline on Day 3 of monotherapy. No serious or Grade 3 (severe) or higher adverse events and no clinically relevant laboratory abnormalities were observed with either compound. **CONCLUSIONS:** ABT-493 and ABT-530 demonstrated potent antiviral activity and acceptable safety during 3-day monotherapy in patients with HCV genotype 1 infection with/without compensated cirrhosis. Based on these results, phase 2 studies assessing the combination of these next generation DAAs for the treatment of chronic HCV infection in patients with and without compensated cirrhosis have been initiated.

**The impact of ribavirin on real-world adherence rates in hepatitis C patients treated with sofosbuvir plus simeprevir,** Walker DR1, Juday TR1, Manthena SR1, Jing Y1, Sood V1. Clinicoecon Outcomes Res. 2015 Dec 17;7:637-42. doi: 10.2147/CEOR.S87261. eCollection 2015.

**BACKGROUND:** Combination therapy with sofosbuvir (SOF) and simeprevir (SIM) is used to treat patients with hepatitis C virus infection. It is currently unknown whether adding ribavirin (RBV) to SOF + SIM, which raises the pill count from two up to eight pills a day, impacts adherence. The aim of this study is to examine the impact of pill count on real-world adherence.
rates in patients treated with SOF + SIM with and without RBV. **METHODS:** This retrospective study assessed composite adherence to SOF and SIM over 12 weeks of treatment for two cohorts of hepatitis C patients: one initiating SOF + SIM therapy, and the other initiating SOF + SIM + RBV therapy. Analyses were conducted using MarketScan® and Optum US commercial pharmacy claims and enrollment data. Adherence was adjusted by treatment regimen, age, sex, co-pay, presence/absence of cirrhosis, treatment history, and Charlson Comorbidity Index. **RESULTS:** There was a significant difference in composite unadjusted and adjusted adherence rates for SOF and SIM for the SOF + SIM vs SOF + SIM + RBV cohorts based on MarketScan data (unadjusted, 92.6% and 89.7%, respectively; P=0.0423; adjusted, 92.2% and 88.7%, respectively; P=0.0176), but not based on Optum data (unadjusted, 94.8% and 95.6%, respectively; P=0.5618; adjusted, 94.8% and 95.1%, respectively; P=0.8589). In the MarketScan and Optum databases, there were no statistical differences in unadjusted and adjusted adherence rates for SOF. Unadjusted and adjusted adherence rates for SIM were mixed, as they were for composite adherence. **CONCLUSION:** The impact of the addition of RBV to SOF + SIM therapy was mixed. The impact of RBV on SOF adherence was not significant in either database.

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**Basic and Applied Science, Pre-Clinical Studies**

**Chemokine Receptors CXCR3 and CCR6 and Their Ligands in the Liver and Blood of Patients with Chronic Hepatitis C.** Arsent’eva NA1, Semenov AV2,3, Lyubimova NE2, et al. Bull Exp Biol Med. 2015 Dec;160(2):252-5. doi: 10.1007/s10517-015-3142-z. Epub 2015 Dec 3. We performed a comprehensive analysis of CCR6 and CXCR3 chemokine receptors and their ligands CCL20/MIP-3α, CXCL9/MIG, CXCL10/IP-10, and CXCL11/ITAC in the liver and blood of patients with chronic hepatitis C at different stages of the disease. TaqMan PCR was used to determine mRNA gene expression of chemokines and their receptors in liver specimens, xMAP multiplex analysis was performed to estimate the concentration of chemokines in blood plasma, and flow cytometry was used to evaluate CCR6 and CXCR3 expression on peripheral blood lymphocyte populations. In the liver of patients with hepatitis C, mRNA expression of CXCL10, CCR6, and CXCR3 genes increases with fibrosis progression in the liver tissue. In the plasma, concentrations of all studied chemokines increased depending on the stage of liver fibrosis, CCR6 and CXCR3 expression was changed in various lymphocyte populations. Thus, chemokines are involved in the immunopathogenesis and fibrogenesis in chronic viral hepatitis C. The results suggest using these chemokines in the diagnosis and prognosis of the disease.

**Monoclonal anti-envelope antibody AP33 protects humanized mice against a patient-derived hepatitis C virus challenge.** Desombere I1,2, Fafi-Kremer S3,4,5,2, Van Houtte F1,2, et al. Hepatology. 2015 Dec 28. doi: 10.1002/hep.28428. [Epub ahead of print] End-stage liver disease caused by hepatitis C virus (HCV) infection is a major indication for liver transplantation. However, immediately after transplantation the liver graft of viremic patients universally becomes infected by circulating virus, resulting in accelerated liver disease progression. Currently available direct-acting antiviral therapies have reduced efficacy in patients with end-stage liver disease and prophylactic strategies to prevent HCV recurrence are still highly needed. In this study we compared the ability of two broadly reactive monoclonal antibodies (mAbs), designated 3/11 and AP33, recognizing a distinct but overlapping epitope in the viral E2 glycoprotein to protect humanized mice from a patient-derived HCV challenge.
Their neutralizing activity was assessed using the HCVpp and HCVcc systems expressing multiple patient-derived envelopes and a human-liver chimeric mouse model. HCV RNA was readily detected in all control mice challenged with a patient-derived HCV genotype 1b isolate, while three out of four AP33-treated mice were completely protected. In contrast, only one out of four 3/11-treated mice remained HCV RNA negative throughout the observation period, while the other three had a viral load that was indistinguishable from that in the control group. The increased in vivo efficacy of AP33 was in line with its higher affinity and neutralizing capacity observed in vitro. **CONCLUSION:** Although mAbs AP33 and 3/11 target the same region in E2, only mAb AP33 can efficiently protect from challenge with a heterologous HCV population in vivo. Since mAb AP33 efficiently neutralizes viral variants that escaped the humoral immune response and re-infected the liver graft of transplant patients, it may be a valuable candidate to prevent HCV recurrence. In addition, our data is valuable for the design of a prophylactic vaccine.

**HIV/HCV COINFECTION**

**CXCL12 rs1029153 Polymorphism Is Associated with the Sustained Virological Response in HIV/Hepatitis C Virus-Coinfected Patients on Hepatitis C Virus Therapy.** Pineda-Tenor D1,2, Jiménez-Sousa MA2, Rallón N3, et al. AIDS Res Hum Retroviruses. 2015 Dec 1. [Epub ahead of print]

The immune response against HIV and hepatitis C virus (HCV) infection partly depends on chemokine-mediated recruitment of specific T cells. CXCL12 polymorphisms have been associated with AIDS progression and survival, but there are no data related to HCV infection. The aim of this study was to determine whether CXCL12 polymorphisms are related so as to achieve sustained virological response (SVR) after HCV therapy with pegylated-interferon-alpha/ribavirin (pegIFN-α/ribavirin) in HIV/HCV-coinfected patients. We carried out a retrospective study in 319 naive patients who started HCV treatment. The CXCL12 (rs266093, rs1029153, and rs1801157) and IL28B (rs12980275) polymorphisms were genotyped by using the GoldenGate assay. Genetic data were analyzed under an additive inheritance model. The overall rates of the SVR were 54.9% (175/319) and 41.5% (90/217) in GT1/4 patients and 83.2% (84/101) in GT2/3 patients. Patients with a favorable CXCL12 rs1029153 T allele had higher SVR rates than patients with the rs1029153 CC genotype (44% CC, 49% CT, and 61.3% TT; \( p = 0.025 \)). No significant results for the rs266093 and rs1801157 polymorphisms were found. Patients harboring the favorable rs1029153 T allele had significantly increased odds of achieving SVR [adjusted odds ratio (aOR) = 1.55; 95% confidence interval (95% CI) = 1.01; 2.40; \( p = 0.047 \)]. Moreover, no significant association was found when the study population was stratified by HCV genotype (data not shown), possibly due to the low number of patients in each group. In conclusion, in this study we found that the favorable CXCL12 rs1029153 T allele seems to be related so as to achieve an SVR in HIV/HCV-coinfected patients on pegIFN-α/ribavirin therapy.

BACKGROUND AND AIMS: Acute hepatitis C virus infections (AHCV) are prevalent among HIV positive men having sex with men (MSM) and generally treated with peginterferon-alfa (pegIFN) and ribavirin (RBV) during 24 weeks. The addition of a protease inhibitor could shorten therapy without loss of efficacy. METHODS: We performed an open label single arm study to investigate the efficacy and safety of a 12-week course of boceprevir, pegIFN and RBV for AHCV genotype 1 infections in 10 Dutch HIV treatment centers. Primary endpoint of the study was achievement of sustained virological response rate at week 12 (SVR12) in patients reaching a rapid viral response at week 4 (RVR4) and SVR12 in the intent to treat (ITT) entire study population was the most relevant secondary endpoint. RESULTS: 127 AHCV patients were screened in 16 months of which 65 AHCV genotype 1 patients were included. After spontaneous clearance in 6 patients and withdrawal before treatment initiation in 2, 57 started therapy within 26 weeks after infection. RVR4 rate was 72%. SVR12 rate was 100% in the RVR4 group. SVR12 rate in the ITT group was 86% and comparable to the SVR12 rate of 84% in 73 historical controls treated for 24 weeks with pegIFN and RBV in the same study centers. CONCLUSION: With the addition of boceprevir to pegIFN and RBV, treatment duration of AHCV genotype 1 can be reduced to 12 weeks without loss of efficacy. Given the high drug costs and limited availability of interferon-free regimens, boceprevir pegIFN and RBV can be considered a valid treatment option for AHCV.


OBJECTIVE: To analyze the role of CD3(+)CD56(+) natural killer (NK)-like T cells in HIV(+) patients with acute hepatitis C. DESIGN: Frequency, phenotype, and anti-hepatitis C virus (HCV) activity of CD3(+)CD56(+) NK-like T cells were studied in 36 HIV(+) patients with acute hepatitis C. As controls, 12 patients with chronic HCV/HIV coinfection, 8 HIV monoinfected patients, and 12 healthy donors were enrolled in this study. METHODS: CD3(+)CD56(+) NK-like T-cell-mediated inhibition of HCV replication was analyzed using the HuH7A2HCVreplicon model. The CD3(+)CD56(+) NK-like T-cell phenotype and interferon (IFN)-γ secretion were studied by flow cytometry. RESULTS: Interleukin 12/interleukin 15 stimulated CD3(+)CD56(+) NK-like T cells from healthy donors effectively block HCV replication in vitro in an IFN-γ dependent manner. Accordingly, we found that blocking of IFN-γ with a specific antibody significantly reduced the antiviral activity of CD3(+)CD56(+) NK-like T cells. However, when CD3(+)CD56(+) NK-like T cells from HIV(+) patients were studied, we found HIV infection to be associated with a significantly impaired IFN-γ production, irrespective of HCV coinfection. Accordingly, CD3(+)CD56(+) NK-like T cells from HIV(+) patients were significantly less effective in blocking HCV replication in vitro than cells from healthy individuals. CONCLUSIONS: Taken together, our data indicate that HIV infection is associated with an impaired anti-HCV activity of CD3(+)CD56(+) NK-like T cells, which might represent a novel mechanism of dysregulated immune response in HIV/HCV-coinfected patients.

Knowing how effective and brief in duration the current HCV medical regimen is, how can we maximize SVR in patients experiencing ‘barriers’ with a quick ‘get in and get out’ treatment approach? What might be some intervention approaches?
The Impact of Direct-Acting Antivirals in the Hepatitis C-Sustained Viral Response in Human Immunodeficiency Virus-Infected Patients With Ongoing Barriers to Care.

BACKGROUND: Access to hepatitis C virus (HCV) medications for human immunodeficiency virus (HIV)-infected patients with ongoing barriers to care is restricted by healthcare payers in the absence of HCV treatment outcomes data in the era of direct-acting antivirals (DAA).

METHODS: Retrospective analysis of HCV treatment outcomes using interferon (IFN)-free DAA regimens and an inclusive treatment protocol in an urban HIV clinic where ongoing barriers to care (drug or alcohol use, psychiatric disease, and/or unstable housing) are common. Then, using logistic regression analysis, we compared the proportion of HIV-infected patients who achieved HCV sustained viral response (SVR) in the pegylated-IFN plus ribavirin (PEG-IFN/RBV, 2008-2011), pegylated-IFN plus ribavirin and telaprevir (PEG-IFN/RBV/PI, 2011-2013), and IFN-free DAA therapy eras (2014). Results are displayed using forest plots.

RESULTS: The proportion of patients who achieved HCV SVR in the PEG-IFN/RBV, PEG-IFN/RBV/PI, and IFN-free DAA therapy eras increased from 38.4% (95% confidence interval [CI], 23.2-53.7) and 48% (95% CI, 28.4-67.6) to 83.3% (95% CI, 70.0-96.7), respectively. Similar proportions of patients with ongoing barriers to care were treated during the PEG-IFN/RBV (25 of 39 [64%]), PEG-IFN/RBV/PI (14 of 25 [56%]), and IFN-free DAA (16 of 30 [53%]) eras. Hepatitis C virus SVR among patients with ongoing barriers to care improved from 40% (95% CI, 21-59) to 76.5% (95% CI, 56-97) in the PEG-IFN/RBV and IFN-free DAA eras, respectively. After stratification for factors associated with HCV SVR such as HCV genotype and cirrhosis, HCV SVR were similar in patients regardless of the presence of ongoing barriers to care. CONCLUSIONS: Using IFN-free DAA and an inclusive HCV treatment protocol, 76.5% of HIV/HCV-treated patients with ongoing barriers to care achieved HCV SVR.

Prognostic Value of the Fibrosis-4 Index in Human Immunodeficiency Virus Type-1 Infected Patients Initiating Antiretroviral Therapy with or without Hepatitis C Virus.

OBJECTIVE: To evaluate the Fibrosis (FIB)-4 index as a predictor of major liver-related events (LRE) and liver-related death (LRD) in human immunodeficiency virus (HIV) type-1 patients initiating combination antiretroviral therapy (cART). DESIGN: Retrospective analysis of a prospective cohort study. SETTING: Italian HIV care centers participating to the ICONA Foundation cohort. PARTICIPANTS: Treatment-naive patients enrolled in ICONA were selected who: initiated cART, had hepatitis C virus (HCV) serology results, were HBsAg negative, had an available FIB-4 index at cART start and during follow up. METHODS: Cox regression models were used to determine the association of FIB4 with the risk of major LRE (gastrointestinal bleeding, ascites, hepatic encephalopathy, hepato-renal syndrome or hepatocellular carcinoma) or LRD. RESULTS: Three-thousand four-hundred seventy-five patients were enrolled: 73.3% were males, 27.2% HCV seropositive. At baseline (time of cART initiation) their median age was 39 years, had a median CD4+ T cell count of 260 cells/μL, and median HIV RNA 4.9 log copies/mL, 65.9% had a FIB-4 <1.45, 26.4% 1.45-3.25 and 7.7% >3.25. Over a follow up of 18,662 person-years, 41 events were observed: 25 major LRE and 16 LRD (incidence rate, IR, 2.2 per 1,000 PYFU [95% confidence interval, CI 1.6-3.0]). IR was
higher in HCV seropositives as compared to negatives (5.9 vs 0.5 per 1,000 PYFU). Higher baseline FIB-4 category as compared to <1.45 (FIB-4 1.45-3.25: HR 3.55, 95% CI 1.09-11.58; FIB-4>3.25: HR 4.25, 1.21-14.92) and time-updated FIB-4 (FIB-4 1.45-3.25: HR 3.40, 1.02-11.40; FIB-4>3.25: HR 21.24, 6.75-66.84) were independently predictive of major LRE/LRD, after adjusting for HIV- and HCV-related variables, alcohol consumption and type of cART. 

CONCLUSIONS: The FIB-4 index at cART initiation, and its modification over time are risk factors for major LRE or LRD, independently of infection with HCV and could be used to monitor patients on cART.

Interferon-Free Treatment of Hepatitis C Virus in HIV/Hepatitis C Virus-Coinfected Subjects Results in Increased Serum Low-Density Lipoprotein Concentration. Townsend K1, Meissner EG1,2,3, Sidharthan S3, et al. AIDS Res Hum Retroviruses. 2015 Dec 15. [Epub ahead of print]

Chronic hepatitis C virus (HCV) infection is associated with lower serum concentration of low-density lipoprotein (LDL-C), the primary cholesterol metabolite targeted pharmaceutically to modulate cardiovascular risk. Chronic infection with human immunodeficiency virus (HIV) and treatment with antiretrovirals (ARVs) are associated with dyslipidemia and increased risk of cardiovascular disease. In subjects coinfected with HIV and HCV, lipid abnormalities associated with either infection alone are often attenuated. Treatment of chronic HCV infection in HIV/HCV-coinfected subjects is now possible with interferon (IFN)-free regimens composed of directly acting antivirals (DAAs). We previously observed a marked increase in serum LDL-C in HCV-monoinfected subjects treated with sofosbuvir and ribavirin (SOF/RBV) that correlated with viral decline in serum, suggesting a direct influence of HCV clearance on serum cholesterol. In the present study, we assessed longitudinal changes in cholesterol in HIV/HCV-coinfected subjects during treatment of HCV genotype-1 (GT1) infection with combination DAA therapy. We report a rapid increase in LDL-C and LDL particle size by week 2 of treatment that was sustained during and after treatment in HIV/HCV-coinfected subjects. No change in serum LDL-C was observed at day 3 of treatment, in spite of a marked reduction in serum HCV viral load, suggesting LDL-C increases do not directly reflect HCV clearance as measured in peripheral blood. After effective DAA therapy for HCV, an increase in LDL should be anticipated in HIV/HCV-coinfected subjects.

Engaging patients in parallel testing for various screenings is an effective time-saving and engagement strategy. What might be some effective slogans or sayings that can be used during screening events to destigmatize screening, thereby maximizing the uptake of screening services? Simultaneous Human Immunodeficiency Virus-Hepatitis B-Hepatitis C Point-of-Care Tests Improve Outcomes in Linkage-to-Care: Results of a Randomized Control Trial in Persons Without Healthcare Coverage. Bottero J1, Boyd A2, Gozlan J3, et al. Open Forum Infect Dis. 2015 Oct 26;2(4):ofv162. doi: 10.1093/ofid/ofv162. eCollection 2015. 

BACKGROUND: In Europe and the United States, more than two thirds of individuals infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) and 15%-30% of human immunodeficiency virus (HIV)-positive individuals are unaware of their infection status. Simultaneous HIV-, HBV-, and HCV-rapid tests could help improve infection awareness and linkage-to-care in particularly vulnerable populations. METHODS: The OptiScreen III study was a single-center, randomized, control trial conducted at a free clinic ("Médecins du Monde", Paris, France). Participants were randomized 1:1 to receive 1 of 2 interventions testing for HIV, HBV, and HCV: standard serology-based testing (S-arm) or point-of-care rapid testing (RT-
The main study endpoints were the proportion of participants who became aware of their HIV, HBV, and HCV status and who were linked to care when testing positive. **RESULTS:** A total of 324 individuals, representing mainly African immigrants, were included. In the S-arm, 115 of 162 (71.0%) participants performed a blood draw and 104 of 162 (64.2%) retrieved their test result. In comparison, 159 of 162 (98.2%) of participants randomized to the RT-arm obtained their results (P < .001). Of the 38 (11.7%) participants testing positive (HIV, n = 7; HBV, n = 23; HCV, n = 8), 15 of 18 (83.3%) in the S-arm and 18 of 20 (90.0%) in the RT-arm were linked-to-care (P = .7). In post hoc analysis assuming the same disease prevalence in those without obtaining test results, difference in linkage-to-care was more pronounced (S-arm = 60.0% vs RT-arm = 90.0%; P = .04). **CONCLUSIONS:** In a highly at-risk population for chronic viral infections, the simultaneous use of HIV, HBV, and HCV point-of-care tests clearly improves the "cascade of screening" and quite possibly linkage-to-care.

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**COMPLEMENTARY AND ALTERNATIVE MEDICINE**


Hepatitis C virus (HCV) infection is the leading cause of chronic liver diseases. Water extracts of the leaves of the wild Egyptian artichoke (WEA) (Cynara cardunculus L. var. sylvestris (Lam.) Fiori) have been used for centuries in Sinai Peninsula to treat hepatitis symptoms. Here, we isolated and characterized six compounds from the water extract of WEA and evaluated their HCV inhibition capacity in vitro. Importantly, two of these compounds namely grosheimol and cynaropicrin inhibited HCV with half maximal effective concentrations (EC50) in the low micromolar range. They inhibited HCV entry into target cells and were active both against cell-free infection as well as cell-cell transmission. Furthermore, the antiviral activity of both compounds was pan-genotypic as HCV genotypes 1a, 1b, 2b, 3a, 4a, 5a, 6a and 7a were inhibited. Thus, grosheimol and cynaropicrin are promising candidates for the development of new pan-genotypic entry inhibitors of HCV infection. **IMPORTANCE:** Because there is no preventive HCV vaccine available today, the discovery of novel anti-HCV cell entry inhibitors could help develop preventive measures of infection. The present study describes two compounds, isolated from the wild Egyptian artichoke (WEA), with respect to their structural elucidation, absolute configuration and quantitative determination. Importantly, both compounds inhibited HCV infection in vitro. The first compound was an unknown molecule and it was designated grosheimol while the second compound is the known molecule cynaropicrin. Both compounds belong to the group of sesquiterpene lactones. The mode-of-action of these compounds was during the early steps of the HCV life cycle, including cell-free and cell-cell infection inhibition. These natural compounds present promising candidates for further development into anti-HCV therapeutics.

**A Phase I Dose Escalation Study Demonstrates Quercetin Safety and Explores Potential for Bioflavonoid Antivirals in Patients with Chronic Hepatitis C.** Lu NT1,2, Crespi CM3,4, Liu NM1, et al. Phytother Res. 2015 Dec 1. doi: 10.1002/ptr.5518. [Epub ahead of print]

The hepatitis C virus (HCV) infects more than 180 million people worldwide, with long-term consequences including liver failure and hepatocellular carcinoma. Quercetin bioflavonoids can
decrease HCV production in tissue culture, in part through inhibition of heat shock proteins. If quercetin demonstrates safety and antiviral activity in patients, then it could be developed into an inexpensive HCV treatment for third world countries or other affected populations that lack financial means to cover the cost of mainstream antivirals. A phase 1 dose escalation study was performed to evaluate the safety of quercetin in 30 untreated patients with chronic HCV infection and to preliminarily characterize quercetin's potential in suppressing viral load and/or liver injury. Quercetin displayed safety in all trial participants. Additionally, 8 patients showed a "clinically meaningful" 0.41-log viral load decrease. There was a positive correlation (r = 0.41, p = 0.03) indicating a tendency for HCV decrease in patients with a lower ratio of plasma quercetin relative to dose. No significant changes in aspartate transaminase and alanine transaminase were detected. In conclusion, quercetin exhibited safety (up to 5 g daily) and there was a potential for antiviral activity in some hepatitis C patients.

Epidemiology, Diagnostics, and Miscellaneous Works

Many providers have not implemented birth-cohort testing, an effective strategy known to identify new patients, due to time constraints or discomfort and hesitancy discussing HCV with their patients. What are some other viable ways to minimize the discomfort around discussing HCV risk factors while still engaging patients in necessary educational discussions, and maximizing the number of patients within the birth cohort receiving HCV testing?


BACKGROUND: International guidelines and U.S. guidelines prior to 2012 only recommended testing for hepatitis C virus (HCV) infection among patients at risk, but adherence to guidelines is poor, and the majority of those infected remain undiagnosed. A strategy to perform one-time testing of all patients born during 1945-1965, birth cohort testing, may diagnose HCV infection among patients whose risk remains unknown. We sought to determine if a birth-cohort testing intervention for HCV antibody positivity helped identify patients with fewer documented risk factors or medical indications than a pre-intervention, risk-based testing strategy. METHODS: We used a cross-sectional design with retrospective electronic medical record review to examine patients identified with HCV antibody positivity (Ab+) during a pre-intervention (risk-based) phase, the standard of care at the time, vs. a birth-cohort testing intervention phase. We compared demographic and clinical characteristics and HCV risk-associated factors among patients whose HCV Ab + was identified during the pre-intervention (risk-based testing) vs. post birth-cohort intervention phases. Study subjects were patients identified as HCV-Ab + in the baseline (risk-based) and birth-cohort testing phases of the Hepatitis C Assessment and Testing (HepCAT) Project. RESULTS: Compared to the risk-based phase, patients newly diagnosed with HCV Ab + after the birth-cohort intervention were significantly less likely to have a history of any substance abuse (30.5 % vs. 49.5 %, p = 0.02), elevated alanine transaminase levels of > 40 U/L (22.0 % vs. 46.7 %, p = 0.002), or the composite any risk-associated factor (55.9 % vs.
CONCLUSIONS: Birth-cohort testing is an useful strategy for identifying previously undiagnosed HCV Ab+ because it does not require providers ask risk-based questions, or patients to disclose risk behaviors, and appears to identify HCV Ab+ in patients who would not have been identified using a risk-based testing strategy.

Understanding that education is ‘vital component in reducing the gaps in HCV knowledge’, what preventative education programs can be implemented in K-12 education systems that will impact students’ future decision-making, which may decrease their risk for HCV acquisition?


BACKGROUND: Baby boomers (people born between 1945 and 1965) are responsible for three-quarters of Hepatitis C (HCV) infections in the US; however, HCV testing is distinctly underused by them. AIM: To assess the status, predictors, and correlates of HCV knowledge among African-American baby boomers (AABBs) in Washington, DC. METHODS: A cross-sectional survey among persons aged 46-69 was conducted using audio computer-assisted self-interviewing (ACASI). Data on HCV knowledge, socio-demographics, prior history of HCV testing, health-related characteristics, HCV vulnerability and HCV treatment perceptions were collected. Descriptive statistics was used to describe the study population. Pearson correlations were used to examine linear associations between HCV knowledge and Health Belief Model constructs related to HCV. Linear regression analysis was conducted to assess the predictors of knowledge. RESULTS: Out of the 137 participants, about sixty percent (60.6%) were females, mean age 59±6.40; 44.8% had at least a college education. The average knowledge score was low (48.7%). HCV knowledge was significantly correlated with constructs of perceived severity and perceived benefits. Age (β= -0.10; p=0.003), and level of education (β=0.93, p=0.027) were significant predictors. CONCLUSIONS: Overall, respondents have a low level of knowledge. The lower level of education and older age were significant predictors of inadequate HCV knowledge. Thus, HCV education among these people may be a vital component in reducing the gaps in HCV knowledge.


Hepatitis C virus (HCV) and human pegivirus (HPgV), formerly GBV-C, are the only known human viruses in the Hepacivirus and Pegivirus genera, respectively, of the family Flaviviridae. We present the discovery of a second pegivirus, provisionally designated human pegivirus 2 (HPgV-2), by next-generation sequencing of plasma from an HCV-infected patient with multiple bloodborne exposures who died from sepsis of unknown etiology. HPgV-2 is highly divergent, situated on a deep phylogenetic branch in a clade that includes rodent and bat pegiviruses, with which it shares <32% amino acid identity. Molecular and serological tools were developed and validated for high-throughput screening of plasma samples, and a panel of 3 independent serological markers strongly correlated antibody responses with viral RNA positivity (99.9% negative predictive value). Discovery of 11 additional RNA-positive samples from a total of 2440 screened (0.45%) revealed 93-94% nucleotide identity between HPgV-2 strains. All 12 HPgV-2 RNA-positive cases were identified in individuals also testing positive for HCV RNA.
(12 of 983; 1.22%), including 2 samples co-infected with HIV, but HPgV-2 RNA was not detected in non-HCV-infected individuals (p<0.0001), including those singly infected by HIV (p = 0.0075) or HBV (p = 0.0077), nor in volunteer blood donors (p = 0.0082). Nine of the 12 (75%) HPgV-2 RNA positive samples were reactive for antibodies to viral serologic markers, whereas only 28 of 2,429 (1.15%) HPgV-2 RNA negative samples were seropositive. Longitudinal sampling in two individuals revealed that active HPgV-2 infection can persist in blood for at least 7 weeks, despite the presence of virus-specific antibodies. One individual harboring both HPgV-2 and HCV RNA was found to be seronegative for both viruses, suggesting a high likelihood of simultaneous acquisition of HCV and HPgV-2 infection from an acute co-transmission event. **Taken together, our results indicate that** HPgV-2 is a novel bloodborne infectious virus of humans and likely transmitted via the parenteral route.

With new drug availability to treat patients with G3, more patients, in theory, can achieve SVR; however, the approval of DAC/SOF often proves difficult due to an additional increased cost since the drugs are made by two different manufacturers. What preemptive measures can organizations take to increase their capacity to address these impending denials? What advocacy efforts are needed to rectify this situation?


Chronic hepatitis C virus (HCV) infection is one of the most common etiologies of liver-related mortality throughout the world. Traditionally, therapy has been focused on pegylated interferon in combination with ribavirin, with clinical trials demonstrating that HCV genotype 1 had the lowest response rate (40-50%), while genotype 3 had an intermediate response rate (60-70%). Recently, significant advances have been made with all-oral direct-acting antiviral (DAA) therapy, which have significantly improved cure rates for HCV genotype 1. Accordingly, HCV genotype 3 is now potentially the most difficult to treat. One of the most potent DAA medications is sofosbuvir, a pan-genotypic nucleotide analogue that inhibits the NS5B polymerase of HCV. Daclatasvir, a pan-genotypic inhibitor of the HCV NS5A replication complex, was recently approved in the United States for treatment of HCV genotype 3 in conjunction with sofosbuvir. This combination may provide a powerful tool in the treatment of HCV genotype 3.


**PURPOSE OF REVIEW:** Combined pegylated interferon-α and ribavirin remains the standard therapy for pediatric hepatitis C virus (HCV) infections in 2016, but direct-acting antivirals (DAAs) with greatly improved efficacy and safety are now approved for adults. Here we review the major classes of DAAs and their anticipated use for treatment and potentially prevention of HCV in children. **RECENT FINDINGS:** Currently approved DAAs target the viral protease, polymerase, and NS5A, a protein involved in viral replication and assembly. In combination, DAAs have lifted sustained virologic response rates in adults to more than 90% for multiple HCV genotypes, and the rich DAA pipeline promises further improvements. Clinical trials of interferon-free DAA regimens have been initiated for children ages 3-17 years. In 2016, the first efficacy trial of a preventive HCV vaccine is also underway. While awaiting a vaccine, there is hope that increased DAA utilization may prevent pediatric HCV infections by shrinking the pool
of infectious persons. **SUMMARY:** Interferon-free DAA regimens have revolutionized therapy for HCV-infected adults and, pending results of pediatric trials, will likely do the same for HCV-infected children. If widely deployed, DAA therapies may also help to reduce the number of new vertically and horizontally acquired pediatric infections.

### Liver Cancer

This data reflects real-world costs for treating patients with liver cancer. What elected officials or key decision makers would you share this information with in order to shed light on the vital importance of addressing liver disease in our communities today, versus waiting until patients develop cancer?

**Direct costs of care for hepatocellular carcinoma in patients with hepatitis C cirrhosis.**

Tapper EB1, Catana AM1, Sethi N1, Mansuri D1, Sethi S1, Vong A1, Afdhal NH1. Cancer. 2015 Dec 30. doi: 10.1002/cncr.29855. [Epub ahead of print]

**BACKGROUND:** Hepatitis C virus (HCV) is the commonest cause of hepatocellular carcinoma (HCC) in the United States. The benefits of HCV therapy may be measured in part by the prevention of HCC and other complications of cirrhosis. The true cost of care of the HCV patient with HCC is unknown. **METHODS:** One hundred patients were randomly selected from a cohort of all HCC patients with HCV at a US transplant center between 2003 and 2013. Patients were categorized by the primary treatment modality, Barcelona class, and ultimate transplant status. Costs included the unit costs of procedures, imaging, hospitalizations, medications, and all subsequent care of the HCC patient until either death or the end of follow-up. Associations with survival and cost were assessed in multivariate regression models. **RESULTS:** Overall costs included a median of $176,456 (interquartile range [IQR], $84,489-$292,192) per patient or $6279 (IQR, $4043-$9720) per patient-month of observation. The median costs per patient-month were $7492 (IQR, $5137-$11,057) for transplant patients and $4830 for nontransplant patients. The highest median monthly costs were for transplant patients with Barcelona A4 disease ($11,349) and patients who received chemoembolization whether they underwent transplantation ($10,244) or not ($8853). Transarterial chemoembolization and radiofrequency ablation were independently associated with a 28% increase and a 22% decrease in costs, respectively, with adjustments for the severity of liver disease and Barcelona class. **CONCLUSIONS:** These data represent real-world estimates of the cost of HCC care provided at a transplant center and should inform economic studies of HCV therapy. Cancer 2015. © 2015 American Cancer Society.

**Hepatocellular carcinoma in cirrhotic versus noncirrhotic livers: results from a large cohort in the Netherlands.**


**OBJECTIVES:** Hepatocellular carcinoma (HCC) usually occurs in patients with cirrhosis, but can also develop in noncirrhotic livers. In the present study we explored associated risk factors for HCC without cirrhosis and compared patient and tumor characteristics and outcomes in HCC patients with and without underlying cirrhosis. **METHODS:** Patients with HCC diagnosed in the period 2005-2012 in five Dutch academic centers were evaluated. Patients were categorized according to the presence of cirrhosis on the basis of histology or combined radiological and laboratory features. **RESULTS:** In total, 19% of the 1221 HCC patients had no underlying cirrhosis. Noncirrhotic HCC patients were more likely to be female and to have nonalcoholic...
fatty liver disease or no risk factors for underlying liver disease, and less likely to have hepatitis C virus or alcohol-related liver disease than did cirrhotic HCC patients. HCCs in noncirrhotic livers were more often unifocal (67 vs. 48%), but tumor size was significantly larger (8 vs. 4 cm). Despite the larger tumors, more patients underwent resection (50 vs. 10%) and overall survival was significantly better than in cirrhotics. In multivariate analyses, absence of cirrhosis [hazard ratio (HR) 0.49, 95% confidence interval (CI) 0.38-0.63] and presence of hepatitis B (HR 0.68, 95% CI 0.51-0.91) were independent predictors for lower mortality, whereas hepatitis C virus was associated with higher mortality (HR 1.32, 95% CI 1.01-1.65). **CONCLUSION:** HCC without cirrhosis was strongly associated with female sex and presence of nonalcoholic fatty liver disease or no risk factors for underlying liver disease. In absence of cirrhosis, resections were more often performed, with better survival despite larger tumor size.


**BACKGROUND:** Hepatitis C virus non-structural protein 5A is known to play a role in development of hepatocellular carcinoma (HCC) via interactions with host cell pathways. **OBJECTIVES:** Hepatitis C virus genotype 1b strains presenting a wide insertion of 31 amino acids in the non-structural protein 5A V3 domain (V3 DI) were studied to determine whether this V3-like additional domain (V3 DII) was associated with HCC occurrence. **STUDY DESIGN:** Seventy-four patients' sera were screened for V3 DII presence regarding clinical status. **RESULTS:** Three strains with duplicated V3 were detected among patients with progression to HCC (n=28), two strains among patients with liver cirrhosis (Ci, n=27) and none among patients with chronic hepatitis (Chr, n=19). Phylogenetic trees built from V3 DI and V3 DII sequences indicated that the latter clustered separately. In between-group clonal analysis, V3 DII sequences from the HCC group were found to be more distant from HCV-J than V3 DI sequences (p<0.0001). Between-group comparisons showed significant differences in genetic distances from HCV-J, in HCC V3 DI and HCC V3 DII compared to Ci V3 DI and Ci V3 DII sequences (p<0.0001). HCC V3 DII domain and its junction with V3 DI exhibited higher Shannon entropy values and enrichment in disorder-promoting residues. **CONCLUSIONS:** Taken together, our results suggest that V3 DII evolution may differ in strains associated with HCC occurrence. The presence of an intrinsically "disordered" V3 duplicate may alter the NS5A protein network. Further investigations are necessary to elucidate the potential impact of V3 duplication in the context of carcinogenesis.


**BACKGROUND:** Hepatitis C virus (HCV) and alcohol abuse are the main risk factors for hepatocellular carcinoma (HCC) in Western countries. **AIM:** To investigate the role of alcoholic
aetiology on clinical presentation, treatment and outcome of HCC as well as on each Barcelona Clinic Liver Cancer (BCLC) stage, as compared to HCV-related HCCs. METHODS: A total of 1642 HCV and 573 alcoholic patients from the Italian Liver Cancer (ITA.LI.CA) database, diagnosed with HCC between January 2000 and December 2012 were compared for age, gender, type of diagnosis, tumour burden, portal vein thrombosis (PVT), oesophageal varices, liver function tests, alpha-fetoprotein, BCLC, treatment and survival. Aetiology was tested as predictor of survival in multivariate Cox regression models and according to HCC stages. RESULTS: Cirrhosis was present in 96% of cases in both groups. Alcoholic patients were younger, more likely male, with HCC diagnosed outside surveillance, in intermediate/terminal BCLC stage and had worse liver function. After adjustment for the lead-time, median (95% CI) overall survival (OS) was 27.4 months (21.5-33.2) in alcoholic and 33.6 months (30.7-36.5) in HCV patients (P = 0.021). The prognostic role of aetiology disappeared when survival was assessed in each BCLC stage and in the Cox regression multivariate models. CONCLUSIONS: Alcoholic aetiology affects survival of HCC patients through its negative effects on secondary prevention and cancer presentation but not through a greater cancer aggressiveness or worse treatment result. In fact, survival adjusted for confounding factors was similar in alcoholic and HCV patients.

High post-treatment absolute monocyte count predicted hepatocellular carcinoma risk in HCV patients who failed peginterferon/ribavirin therapy. Chen TM1,2, Lin CC3,4, Huang PT5, Wen CF6. Tumour Biol. 2015 Dec 12. [Epub ahead of print] Salient studies have investigated the association between host inflammatory response and cancer. This study was conducted to test the hypothesis that peripheral absolute monocyte counts (AMC) could impart an increased risk of hepatocellular carcinoma (HCC) development in hepatitis C virus (HCV)-infected patients after a failed peginterferon/ribavirin (PR) combination therapy. A total of 723 chronic HCV-infected patients were treated with PR, of which 183 (25.3 %) patients did not achieve a sustained virological response (non-SVR). Post-treatment AMC values were measured at 6 months after end of PR treatment. Fifteen (2.8 %) of 540 patients with an SVR developed HCC during a median follow-up period of 41.4 months, and 14 (7.7 %) of 183 non-SVR patients developed HCC during a median follow-up of 36.8 months (log rank test for SVR vs. non-SVR, P = 0.002). Cox regression analysis revealed that post-treatment AFP level (HR 1.070; 95 % CI = 1.024-1.119, P = 0.003) and post-treatment aspartate aminotransferase (AST)-to-platelet ratio index (APRI) ≥0.5 (HR 4.401; 95 % CI = 1.463-13.233, P = 0.008) were independent variables associated with HCC development for SVR patients. For non-SVR patients, diabetes (HR 5.750; 95 % CI = 1.387-23.841, P = 0.016), post treatment AMC ≥370 mm-3 (HR 5.805; 95 % CI = 1.268-26.573, P = 0.023), and post-treatment APRI ≥1.5 (HR 10.905; 95 % CI = 2.493-47.697, P = 0.002) were independent risks associated with HCC. In conclusion, post-treatment AMC has a role in prognostication of HCC development in HCV-infected patients who failed to achieve an SVR after PR combination therapy.


BACKGROUND: A sustained virological response (SVR) to interferon (IFN) therapy for chronic hepatitis C virus (HCV) reduces but does not eliminate the risk of hepatocellular
carcinoma (HCC). The prognosis after hepatectomy for HCC in patients with SVR has not been fully clarified. PATIENTS AND METHODS: Between 1998 and 2011, 494 patients with chronic hepatitis C underwent hepatic resection for HCC at four high-volume Centers in Japan. Out of these, 188 underwent IFN therapy for HCV. In 92 patients, SVR to IFN therapy had been achieved at the time of hepatectomy (SVR group) while in 96 patients, SVR had not (non-SVR group) had not been achieved. In the other 306 patients, IFN therapy had never been performed at all (no IFN group). The clinicopathological factors and long-term outcomes were retrospectively reviewed and compared among SVR, non-SVR and no IFN groups. RESULTS: The mean time from achievement of SVR to hepatectomy for HCC was 6.2 years (range=2 months to 20 years). The preoperative serum alanine transaminase, albumin, prothrombin time, indocyanine green retention test at 15 min were significantly preserved in the SVR group. The overall survival and recurrence-free survival rates were significantly higher in the SVR group compared to patients in non-SVR and no IFN groups. CONCLUSION: In patients undergoing hepatectomy for HCC, those with SVR had good liver function and a more favorable long-term prognosis than those without SVR. Early detection of HCC after SVR and meticulous hepatectomy with small blood loss is important in patients with HCC after hepatectomy.