
BACKGROUND AND STUDY AIM: Concomitant hepatitis C virus (HCV) infection and psoriasis vulgaris (PV) are not uncommon coexisting diseases, especially in areas with high viral hepatitis endemicity. To date, data about the interaction between both diseases are scarce. Therefore, we aimed to describe the possible interplay between the HCV viral load and psoriatic activity in concomitant Egyptian diseased patients.

PATIENTS AND METHODS: Between December 2011 and August 2013, all psoriatic patients attending Assiut University Hospital outpatient clinics were tested for HCV serologic assay. Patients with positively coexisting diseases were further reevaluated for psoriasis area severity index (PASI) score assessment, liver function tests, HCV-RNA-polymerase chain reaction (PCR) assays, and sonographic examination of the liver. For comparative purposes, another matched group (n=26) with psoriasis only (HCV-negative group) was enrolled as a control.

RESULTS: During the period of the study, 20 patients with concomitant PV and HCV infection (HCV-positive group; 50% males, mean age of 44.15±10.66years) were recruited. The mean PASI score was 44.75±10.38 and clinical signs of liver dysfunction were observed in 40% (n=8), 100% had abnormal liver function tests (n=20), and 75% had sonographic findings of cirrhosis (n=15). The PASI score was significantly higher in the HCV-positive psoriatic group compared to the HCV-negative control (p<0.001). Significant correlations were detected between the PASI score and the viral loads, and also with alanine aminotransferase (ALT).

CONCLUSION: When HCV was found concomitantly with PV, a high possibility of severe disease pattern will be expected that entails special precautions in the treatment process.


The burden of hepatitis C virus genotype 4 (HCV-4) is high in Africa and East Mediterranean countries. Previous reports estimate sustained virologic response (SVR) rates in HCV-4 to be ~20-70%. However, many of these studies are limited by different study designs and small sample sizes. Our aim was to evaluate treatment outcome and host/viral factors on SVR in HCV-4 patients treated with pegylated interferon and ribavirin (PEG IFN+RBV) in a systematic and quantitative manner. A comprehensive literature search in MEDLINE and EMBASE for 'genotype 4' was conducted in November 2013. Abstracts from American Association for the Study of Liver
Diseases, Asian Pacific Study of the Liver, Digestive Disease Week, and European Association for the Study of the Liver in 2012/2013 were reviewed. Inclusion criteria were original studies with at least 25 treatment-naive HCV-4 patients treated with PEG IFN+RBV. Exclusion criteria were coinfection with HIV, hepatitis B virus, or other genotypes. Effect sizes were calculated using random-effects models. Heterogeneity was determined by Cochrane Q-test (P<0.05) and I statistic (>50%). We included 51 studies (11 102 HCV-4 patients) in the primary analysis. Pooled SVR was 53% [95% confidence interval (CI): 50-55%] (Q-statistic=269.20, P<0.05; I=81.43). On subgroup analyses, SVR was significantly associated with lower viral load, odds ratio (OR) 3.05 (CI: 1.80-5.17, P<0.001); mild fibrosis, OR 3.17 (CI: 2.19-4.59, P<0.001); and favorable IL28B polymorphisms, rs12979860 CC versus CT/TT, OR 4.70 (CI: 2.87-7.69, P<0.001), and rs8099917 TT versus GT/GG, OR 5.21 (CI: 2.31-11.73, P<0.001). HCV-4 patients treated with PEG IFN+RBV may expect SVR rates of ~50%. Lower viral load, mild fibrosis, and favorable IL28B (rs12979860 CC and rs8099917 TT) are positively associated with SVR.


The number of children affected by the hepatitis C virus (HCV) in the United States is estimated to be between 23000 to 46000. The projected medical cost for children with HCV in the United States is $199-366 million over the next decade. The implementation of routine screening of blood supply has virtually eliminated transmission via transfusion and vertical transmission is now the most common mode of infection in children. Infections acquired during infancy are more likely to spontaneously resolve and fibrosis of the liver tends to increase with age suggesting slow progressive histologic injury. Anti-viral treatment may be warranted in children with persistently elevated liver enzymes or with significant fibrosis on liver biopsy. Current standard of care includes weekly pegylated interferon and ribavirin twice daily. Predictors of high sustained viral response include genotype 2 and 3 and low viral load in children with genotype 1 (< 600000 IU/mL). Phase 1 and 2 trials with triple therapy (interferon, ribavirin, and a protease inhibitor) are ongoing. Triple therapy is associated with a significantly higher rate of sustained virologic response (> 90%). Only 34 pediatric patients were transplanted with hepatitis C between January 2008 and April 2013. The majority of pediatric patients were born prior to universal screening of blood products and, as of June 2013, there are only two pediatric patients awaiting liver transplantation for end-stage liver disease secondary to hepatitis C. Pediatric survival rates post-transplant are excellent but graft survivals are noticeably reduced compared to adults (73.73% for pediatric patients at one year compared to 87.69% in adult patients). New safe and effective antiviral therapies for recurrent HCV should help increase graft survival.


INTRODUCTION:: We performed a pilot study examining the safety and tolerability of valacyclovir in veterans with herpes simplex virus type 2 and hepatitis C virus (HCV) coinfection. METHODS:: We performed a randomized double-blind, placebo-controlled, crossover clinical trial in U.S. veterans with genotype 1 HCV/herpes simplex virus type 2 coinfection. Patients were randomized 1:1 in blocks of 10 to receive either 1 g twice-daily valacyclovir or matching placebo for 8 weeks followed by a 2-week washout phase with daily placebo. The alternate therapy (valacyclovir or placebo) was given for an additional 8-week period. Safety assessments were performed every 2
weeks. Changes in HCV RNA and alanine aminotransferase (ALT) were estimated using linear mixed models (SAS Proc Mixed). RESULTS: Thirty patients were enrolled. Valacyclovir was not associated with toxicity or adverse events. ALT levels declined 6% to 10%; mean HCV RNA levels were reduced 24% (1.3 million IU/mL [0.21 log10 IU/mL]) during the valacyclovir phase (P = 0.08) with no carryover effect observed (P = 0.21). CONCLUSIONS: Valacyclovir 1 g twice daily showed no evidence of hepatotoxicity in U.S. veterans with hepatitis C. A modest reduction in serum levels of ALT and plasma levels of HCV RNA was observed.


BACKGROUND AND AIMS: Early recognition of prediabetes can lead to timely clinical interventions to prevent type 2 diabetes. Both Latino ethnicity and chronic hepatitis C (HCV) have been identified as diabetic risk factors. We aimed to investigate predictors of impaired fasting glucose (IFG), a common prediabetic state, among Latinos with and without HCV. METHODS: One hundred Latino adults with no history of diabetes or cirrhosis underwent clinical, laboratory, and metabolic evaluation, including oral glucose tolerance testing (OGTT) and insulin suppression testing to quantify directly measured insulin resistance (IR). Isolated IFG was defined as fasting glucose ≥100mg/dL and <140mg/dL at 2 hours with normal glucose tolerance during OGTT. RESULTS: Overall subject characteristics included median age 44 years, 64% male, 40% HCV-positive, and 32% with isolated IFG. Factors associated with isolated IFG included subject age (OR 2.42 per decade, 95%CI 1.40-3.90, p=0.001), HCV infection (OR 4.0, 95%CI 1.71-9.72, p=0.002), and alanine aminotransferase (ALT) (OR 2.35 per doubling, 95%CI 1.46-3.77, p<0.0001). Multipredictor logistic regression analysis identified ALT (OR 2.05 per doubling, p=0.005, 95% CI 1.24-3.40) and age (OR 2.20 per 10 years, p=0.005, 95%CI 1.27-3.80) as factors independently associated with IFG. While HCV was associated with 4-fold higher odds of IFG, this entire effect was mediated by ALT. CONCLUSIONS: We found strong evidence that liver inflammation is a risk factor for prediabetes among Latinos with and without HCV. Among HCV-infected individuals, early antiviral therapy could mitigate the effect of inflammation and represent an important intervention to prevent diabetes in this at-risk population.


OBJECTIVES: To evaluate the progression of fibrosis and factors influencing this in interferon (IFN) treatment-naive Chinese plasma donors infected with hepatitis C virus (HCV) for approximately 20 years. METHODS: From July 2010 to June 2011, we investigated 122 IFN treatment-naive chronic hepatitis C (CHC) patients infected by plasma donation in 1992-1995. Liver fibrosis stage and inflammation grade were evaluated by Metavir and Scheuer scoring systems, respectively. RESULTS: One hundred and twenty patients underwent liver biopsy. Liver biopsy was not performed in one patient with cirrhosis due to ascites, and another patient was excluded because of an invalid biopsy specimen. Cirrhosis was observed in three patients (fibrosis stage F4 in two patients revealed by biopsy, and one patient with ascites confirmed by physical and Doppler ultrasound examination). Fibrosis stages F1 and F2 were present in 55 and 50 patients, respectively. The severity of liver inflammation was independently related to moderate to severe fibrosis (F ≥2). Older age and male sex showed an increasing tendency for more severe fibrosis (F3/F4) in the present cohort. CONCLUSIONS: Based on histopathology results, the progression of fibrosis in patients with CHC infected by repeated plasma donation is slow after HCV infection of
Fatigue during treatment for hepatitis C virus: results of self-reported fatigue severity in two Phase IIb studies of simeprevir treatment in patients with hepatitis C virus genotype 1 infection. Scott J1, Rosa K, Fu M, et al. BMC Infect Dis. 2014 Aug 26;14(1):465. doi: 10.1186/1471-2334-14-465. **BACKGROUND:** Fatigue is a common symptom of chronic hepatitis C virus (HCV) infection and a frequent side-effect of peginterferon/ribavirin (PR) therapy for HCV. This study evaluated the impact of adding the oral HCV NS3/4A protease inhibitor simeprevir to PR on patient-reported fatigue and health status among patients with chronic HCV genotype 1 infection enrolled in the Phase IIb PILLAR and ASPIRE trials [NCT00882908; NCT00980330].

**METHODS:** Treatment-naïve patients (PILLAR, n = 386) and treatment-experienced patients (ASPIRE, n = 462) were randomized to simeprevir plus PR (simeprevir/PR) or placebo plus PR (placebo/PR). In PILLAR, duration of PR treatment in the simeprevir/PR groups was determined using response-guided therapy (RGT) criteria. PR could be terminated at Week 24, instead of Week 48, if HCV RNA was <25 IU/mL by Week 4 and then undetectable at Weeks 12, 16, and 20. In both studies, patients completed the Fatigue Severity Scale (FSS) and EQ-5D quality-of-life questionnaire in their native language at baseline and throughout the studies up until Week 72.

**RESULTS:** During the first 24 weeks of treatment, mean FSS total score was increased to a similar degree compared with baseline among patients receiving simeprevir/PR or placebo/PR in both studies indicating increased fatigue severity. Mean FSS scores returned to values comparable with baseline among patients receiving simeprevir/PR after Week 24 in PILLAR (after treatment completion for the majority of patients) and in ASPIRE (after Week 48), consistent with RGT enabling early termination of all treatment at Week 24 in 82.2% of simeprevir/PR-treated patients in the PILLAR study. Similar results were observed for EQ-5D, with simeprevir/PR-treated patients experiencing less time with worse health problems according to EQ-5D scores compared with placebo/PR groups in both studies, and more rapid improvement in health status associated with shorter treatment duration in the PILLAR study. **CONCLUSIONS:** Combination of simeprevir with PR did not increase patient-reported fatigue severity or health status impairments beyond that reported by patients treated with PR alone. Many patients treated with simeprevir/PR returned to pretreatment fatigue and health status levels sooner due to increased treatment efficacy that enabled shorter duration of all therapy, compared with PR alone.


**BACKGROUND AND AIMS:** There is evidence for an association between thrombosis in the hepatic microcirculation and liver fibrosis. The aim of this study was to evaluate the role of daily low-dose aspirin (75 or 100mg, given for prevention of hepatic artery thrombosis) in fibrosis progression to ≥ F2 fibrosis score in liver-transplant recipients with recurrent hepatitis C virus (HCV). **METHODS:** All HCV-positive patients who had undergone liver transplantation (LT) between 2000 and 2010 were included. Exclusion criteria were negative HCV RNA, previous LT or death within a year of LT. Liver fibrosis was assessed by histological evaluation. Data were censored at the date of the last histological evaluation before starting anti HCV therapy. Progression to fibrosis F ≥ 2 was analyzed with a multistate model with time-dependent covariables. **RESULTS:** One hundred and eighty-eight patients were included. In univariate analysis, older recipient and
donor age, male donor gender, activity score ≥ A2 after LT, number of steroid boluses and aspirin intake (HR: 0.75 [0.57-0.97]; P=0.03) influenced the risk of progression to fibrosis ≥ F2. In multivariate analysis, adjusted on site, older donor age, male donor gender, activity score ≥ A2 and number of steroids boluses, remained independent predictors of fibrosis progression, while younger recipient age and aspirin intake (HR: 0.65 [0.47-0.91]; P=0.01) were associated with a slower fibrosis progression. **CONCLUSION:** Low-dose aspirin treatment might be associated with a lower risk of liver fibrosis progression in patients with HCV recurrence after LT.


To determine stage of liver disease at initial diagnosis of hepatitis C virus (HCV) infection, we analyzed data from the Chronic Hepatitis Cohort Study (CHeCS), a large US observational study. We examined the temporal relationships of initial HCV infection diagnosis with cirrhosis—defined by liver biopsy or mean FIB-4 score >5.88—and time to onset of cirrhotic decompensation in electronic medical records. We determined time in health system prior to HCV diagnosis and rates of hospitalization and death following HCV diagnosis. Of 14,717 patients with chronic HCV seen during 2006-2011, 6,166 (42%) had a definable time of initial HCV diagnosis. Of these, 1,056 (17%) patients met our definition for "late diagnosis" with either cirrhosis concurrent with initial HCV diagnosis (n=550), a first diagnosis of hepatic decompensation before or within 12 months after initial HCV diagnosis (n=506), or both (n=314). Patients with late diagnosis had an average of 6 years in the health system before their HCV diagnosis. In a comparison with patients without late diagnosis, hospitalization (59% vs 35%) and death (33% vs 9%) were more frequent among patients with late diagnosis. Among all who died, mean (median) time from initial HCV diagnosis to death was 4.8 (4.2) years. Conclusion. Many CHeCS patients had advanced liver disease concurrent with their initial HCV diagnosis despite many years of engagement with the health care system, and these patients had high rates of hospitalization and mortality. (Hepatology 2014).


**SUMMARY** Monitoring infections and risk in people who inject drugs (PWID) is important for informing public health responses. In 2011, a novel hepatitis C antibody (anti-HCV) avidity-testing algorithm to identify samples compatible with recent primary infection was introduced into a national surveillance survey. PWID are recruited annually, through >60 needle-and-syringe programmes and prescribing services. Of the 980 individuals that could have been at risk of HCV infection, there were 20 (2%) samples that were compatible with recent primary infection. These were more common among: those imprisoned ≥5 times [8/213; adjusted odds ratio (aOR) 8·7, 95% confidence interval (CI) 2·04-37·03]; women (8/230; aOR 3·8, 95% CI 1·41-10·38); and those ever-infected with hepatitis B (5/56; aOR 6·25, 95% CI 2·12-18·43). This study is the first to apply this algorithm and to examine the risk factors associated with recently acquired HCV infection in a national sample of PWID in the UK. These findings highlight underlying risks and suggest targeted interventions are needed.

Hepatitis C virus (HCV) infection remains common among patients undergoing regular dialysis and good evidence supports the detrimental role of HCV on survival in patients undergoing maintenance dialysis. According to an updated meta-analysis of clinical studies (n=15; 195,370 unique patients on maintenance dialysis), the summary estimate for adjusted relative risk (all-cause mortality) with anti-HCV across the published studies was 1.32 with a 95% Confidence Intervals of 1.24; 1.42, homogeneity assumption was not rejected. Various mechanisms support the excess death risk of HCV-infected patients on regular dialysis, in addition to liver disease-related mortality. The adjusted relative risk for cardiovascular mortality among HCV-infected patients on regular dialysis was 1.26 (95% Confidence Intervals, 1.10; 1.45); the increased cardiovascular mortality in anti-HCV positive patients has been associated in part to malnutrition and chronic inflammation. The current standard of care for HCV in dialysis population is combined antiviral therapy (pegylated interferon plus ribavirin) with a rate of viral response of around 60%. Triple therapy with telaprevir proved to be effective and safe in dialysis patients with HCV but only anecdotal evidence exists. Antiviral treatment of HCV-infected patients on maintenance dialysis could lead to cure the liver damage and the extrahepatic complications. The future availability of all-oral interferon/ribavirin free regimens for antiviral treatment of HCV will help nephrologists to improve survival in this high-risk group.

**Effectiveness of Telaprevir and Boceprevir Triple Therapy for Patients with Hepatitis C Virus Infection in a Large Integrated Care Setting.** Price JC1, Murphy RC, Shvachko VA, et al. Dig Dis Sci. 2014 Aug 8. [Epub ahead of print]

**BACKGROUND:** In 2011, the FDA approved telaprevir (TVR) and boceprevir (BOC) for use with pegylated interferon and ribavirin to treat hepatitis C virus (HCV) genotype 1. We aimed to evaluate the real-world application, tolerability, and effectiveness of TVR- and BOC-based HCV treatment in a large integrated care setting.

**METHODS:** We utilized Northern California Kaiser Permanente Medical Care Program (KPNC) electronic databases and medical records to study the experience of all KPNC patients who initiated TVR or BOC from June 2011 to March 2012.

**RESULTS:** Compared with the pool of 5,194 treatment-eligible patients, the 352 treatment initiators were more likely to be cirrhotic (24 vs. 10 %, p < 0.001) and treatment-experienced (44 vs. 22 %, p < 0.001). Among the treatment initiators, 211 received TVR and 141 BOC. Overall, 31 % discontinued treatment prematurely; 16 % of patients stopped treatment early because of side effects. One patient with cirrhosis died of sepsis during treatment. Premature discontinuation was highest among TVR-treated cirrhotic patients (58 %). Sustained virologic response (SVR) was achieved in 55 % overall and was similar comparing the TVR (56 %)- and BOC (53 %)-treated groups. The only independent predictors of treatment failure were cirrhosis at baseline [odds ratio (OR) for SVR 0.44, p = 0.004] and prior partial or null response (OR for SVR 0.57, p = 0.02).

**CONCLUSIONS:** In the initial application of TVR and BOC, patients with cirrhosis and prior treatment failure were prioritized for treatment. In this real-world experience, most patients successfully completed a full treatment course. However, side effect-related premature discontinuations were common, and SVR rates were lower than reported in clinical trials.

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


**BACKGROUND:** Despite the availability of several direct acting antivirals (DAA) specifically inhibiting different hepatitis C virus (HCV) proteins, treatment of chronic HCV infection is still a challenge also because of the possible selection of resistant viral variants under DAA therapy. Indeed, only the emergence of viruses resistant to the nucleoside inhibitors of the HCV NS5B
polymerase (Pol) has not yet been reported, in spite of the fact that in vitro studies have clearly shown that an S282T amino acid change in the Pol protein may confer resistance to these drugs. On the basis of a previous study showing that viral variants resistant to the HCV protease inhibitors are largely present in the liver - but not in the serum - of untreated patients, we investigated the possible natural occurrence of viral populations with the S282T change in the polymerase protein, analyzing viral isolates from liver and serum of HCV genotype 1b naïve patients. METHODS: HCV-1b isolates from liver specimens and serum samples of 10 chronic hepatitis C patients were analyzed by cloning and sequencing. RESULTS: The S282T mutation was not found in any of the viral isolates from either liver or serum samples of all the cases, although a S282G mutation of unknown virological/clinical relevance was detected in 2/19 liver isolates from one patient. CONCLUSIONS: Our study confirms that the natural selection of the S282T mutation is a rare event, thus explaining the lack of emergence and takeover of these variants under drug pressure.


Hepatitis C virus (HCV) assembles its replication complex on cytosolic membrane vesicles often clustered in a membranous web (MW). During infection, HCV NS5A protein activates PI4KIIIz enzyme, causing massive production and redistribution of phosphatidylinositol 4-phosphate (PI4P) lipid to the replication complex. However, the role of PI4P in HCV lifecycle is not well understood. We postulated that PI4P recruits host effectors to modulate HCV genome replication or virus particles production. To test this hypothesis, we generated cell lines for doxycycline-inducible expression of shRNAs targeting PI4P effector, four-phosphate adaptor protein 2 or FAPP2. FAPP2 depletion attenuated HCV infectivity and impeded HCV RNA synthesis. Indeed, FAPP2 has two functional lipid-binding domains specific for PI4P and glycosphingolipids. While expression of the PI4P-binding mutant protein was expected to inhibit HCV replication, a marked drop in replication efficiency was unexpectedly observed with the glycosphingolipid-binding mutant protein. These data suggest that both domains are crucial for the role of FAPP2 in HCV genome replication. We also found that HCV significantly increases the level of some glycosphingolipids, whereas adding these lipids to FAPP2 depleted cells partially rescued replication, further arguing for the importance of glycosphingolipids in HCV RNA synthesis. Interestingly, FAPP2 is redistributed to the replication complex (RC) characterized by HCV NS5A, NS4B or dsRNA foci. Additionally, FAPP2 depletion disrupts the RC and alters the co-localization of HCV replicase proteins. Altogether, our study implies that HCV co-opts FAPP2 for virus genome replication via PI4P-binding and glycosphingolipids transport to the HCV RC. IMPORTANCE: Like most viruses with a positive sense RNA genome, HCV replicates its RNA on remodeled host membranes composed of lipids hijacked from various internal membrane compartments. During infection, HCV induces massive production and retargeting of the PI4P lipid to its replication complex. However, the role of PI4P in HCV replication is not well understood. In this study, we have shown that FAPP2, a PI4P effector and glycosphingolipid-binding protein, is recruited to the HCV replication complex, required for HCV genome replication and replication complex formation. More importantly, this study demonstrates for the first time, the crucial role of glycosphingolipids in HCV lifecycle and suggests a link between PI4P and glycosphingolipids in HCV genome replication.

Passage of hepatitis C virus (HCV) in human hepatoma cells resulted in populations that displayed partial resistance to IFN-α, telaprevir, daclatasvir, cyclosporine A and ribavirin, despite no prior exposure to these drugs. Mutant spectrum analyses and kinetics of virus production in the absence and presence of drugs indicate that resistance is not due to the presence of drug-resistance mutations in the mutant spectrum of the initial or passaged populations, but to increased replicative fitness acquired during passage. Fitness increase did not alter host factors that lead to shutoff of general host cell protein synthesis and preferential translation of HCV RNA. The results imply viral replicative fitness as a mechanism of multidrug resistance in HCV. **IMPORTANCE**: Viral drug resistance is usually attributed to the presence of amino acid substitutions in the protein targeted by the drug. In the present study with HCV we show that high viral replicative fitness can confer a general drug resistance phenotype to the virus. The results exclude that genomes with drug resistance mutations are responsible for the observed phenotype. The fact that replicative fitness can be a determinant of multidrug resistance may explain why in prolonged chronic HCV infections that favor replicative fitness increase, the virus is less sensitive to drug treatments.

**HIV/HCV COINFECTION**


**INTRODUCTION**: Hepatitis C virus (HCV)/HIV-coinfected patients are at an increased risk of progression of liver disease. Consequently, they benefit most from sustained virological response (SVR) to treatment against HCV. However, SVR rates to pegylated IFN plus ribavirin are disappointingly low in HIV/HCV coinfection. Nevertheless, therapy against HCV is rapidly changing due to the advent of directly acting antiviral drugs against HCV (DAA). Now, high SVR rates can be obtained in HIV/HCV coinfection with DAA regimens. **AREAS COVERED**: Data on DAAs in advanced stages of development in HIV/HCV coinfection, those that have entered Phase III clinical trials in this particular subset, are summarized. A search of clinicaltrials.gov was done to identify DAAs entering Phase III trials that included HIV/HCV-coinfected patients. **EXPERT OPINION**: HCV cure is possible in a high proportion of HIV-coinfected patients with currently available DAA. Caveats of first-generation DAAs are mostly solved by next-generation DAAs. Thus, all-oral regimens under development may be close to the ideal HCV therapy for HIV-coinfected patients. However, the elevated cost of newer DAAs can limit their access.

PPARγ2 Pro12Ala polymorphism was associated with favorable cardiometabolic risk profile in HIV/HCV coinfected patients: a cross-sectional study. García-Broncano P, Berenguer J, Fernández-Rodríguez A, et al. J Transl Med. 2014 Aug 27;12(1):235. doi: 10.1186/s12967-014-0235-9. **BACKGROUND**: Peroxisome proliferator-activated receptor gamma-2 gene (PPARγ2) rs1801282 (Pro12Ala) polymorphism has been associated with lower risk of metabolic disturbance and atherosclerosis. The aim of this study was to analyze the association between the Pro12Ala polymorphism and cardiometabolic risk factors in human immunodeficiency virus (HIV)/Hepatitis C virus (HCV)-coinfected patients. **METHODS**: We carried out a cross-sectional study on 257 HIV/HCV coinfected patients. PPARγ2 polymorphism was genotyped by GoldenGate® assay. The main outcome measures were: i) serum lipids (cholesterol, triglycerides, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), LDL-C/HDL-C, and atherogenic index (Al)); ii) homeostatic model assessment (HOMA-IR) values; iii) serum adipokines (leptin, adiponectin, resistin, plasminogen activator inhibitor-1 (PAI-1), hepatic growth factor (HGF), and nerve growth factor (NGF)). Generalized Linear Models (GLM) with gamma distribution (log-link) were used to
investigate the association between PPARγ2 polymorphism and continuous outcome variables. This test gives the differences between groups and the arithmetic mean ratio (AMR) in continuous outcome variables between groups. **RESULTS:** The rs1801282 CG/GG genotype was associated with low values of cholesterol (adjusted arithmetic mean ratio (aAMR) = 0.87 (95% of confidence interval (95% CI) = 0.79; 0.96); p = 0.004) and LDL-C (aAMR = 0.79 (95% CI = 0.68; 0.93); p = 0.004). Furthermore, rs1801282 CG/GG was associated with low values of HOMA-IR (aAMR = 0.69 (95% CI = 0.49; 0.98); p = 0.038) among patients with significant liver fibrosis (F ≥ 2). Moreover, rs1801282 CG/GG was also associated with low serum values of hepatic growth factor (HGF) (aAMR = 0.61 (95% CI = 0.39; 0.94); p = 0.028), and nerve growth factor (NGF) (aAMR = 0.47 (95% CI = 0.26; 0.84); p = 0.010). The serum levels of leptin, adiponectin, resistin, and PAI-1 did not show significant differences. **CONCLUSIONS:** The presence of PPARγ2 rs1801282 G allele (Ala variant) was associated with a protective cardiometabolic risk profile versus CC genotype in HIV/HCV-coinfected patients. Thus, PPARγ2 rs1801282 polymorphism may play a significant role in the development of metabolic disorders in HIV/HCV coinfected patients, and might have an influence on the cardiovascular risk.

**Distinct patterns of hepcidin and iron regulation during HIV-1, HBV, and HCV infections.**


During HIV type-1 (HIV-1), hepatitis C virus (HCV), and hepatitis B virus (HBV) infections, altered iron balance correlates with morbidity. The liver-produced hormone hepcidin dictates systemic iron homeostasis. We measured hepcidin, iron parameters, cytokines, and inflammatory markers in three cohorts: plasma donors who developed acute HIV-1, HBV, or HCV viremia during the course of donations; HIV-1-positive individuals progressing from early to chronic infection; and chronically HIV-1-infected individuals (receiving antiretroviral therapy or untreated). Hepcidin increased and plasma iron decreased during acute HIV-1 infection, as viremia was initially detected. In patients transitioning from early to chronic HIV-1 infection, hepcidin in the first 60 d of infection positively correlated with the later plasma viral load set-point. Hepcidin remained elevated in individuals with untreated chronic HIV-1 infection and in subjects on ART. In contrast to HIV-1, there was no evidence of hepcidin up-regulation or hypoferremia during the primary viremic phases of HCV or HBV infection; serum iron marginally increased during acute HBV infection. In conclusion, hepcidin induction is part of the pathogenically important systemic inflammatory cascade triggered during HIV-1 infection and may contribute to the establishment and maintenance of viral set-point, which is a strong predictor of progression to AIDS and death. However, distinct patterns of hepcidin and iron regulation occur during different viral infections that have particular tissue tropisms and elicit different systemic inflammatory responses. The hypoferremia of acute infection is therefore a pathogen-specific, not universal, phenomenon.

**Hepatitis C virus core protein enhances HIV-1 replication in human macrophages through TLR2, JNK, and MEK1/2-dependent upregulation of TNF-α and IL-6.**


Despite their differential cell tropisms, HIV-1 and HCV dramatically influence disease progression in coinfected patients. Macrophages are important target cells of HIV-1. We hypothesized that secreted HCV core protein might modulate HIV-1 replication. We demonstrate that HCV core significantly enhances HIV-1 replication in human macrophages by upregulating TNF-α and IL-6 via TLR2-, JNK-, and MEK1/2-dependent pathways. Furthermore, we show that TNF-α and IL-6
secreted from HCV core-treated macrophages reactivates monocytic U1 cells latently infected with HIV-1. Our studies reveal a previously unrecognized role of HCV core by enhancing HIV-1 infection in macrophages.


**BACKGROUND:** Directly Acting Antivirals (DAAs) are predicted to transform hepatitis C (HCV) therapy, yet little is known about the prevalence of naturally occurring resistance mutations in recently acquired HCV. This study aimed to determine the prevalence and frequency of drug resistance mutations in the viral quasispecies among HIV positive and negative individuals with recent HCV. **METHODS:** The NS3 protease, NS5A and NS5B polymerase genes were amplified from fifty genotype 1a participants of the Australian Trial in Acute Hepatitis C. Amino acid variations at sites known to be associated with possible drug resistance were analysed by ultra-deep pyrosequencing. **RESULTS:** Twelve percent of individuals harbourred dominant resistance mutations, while 36% demonstrated non dominant resistant variants below that detectable by bulk sequencing (ie < 20%) but above a threshold of 1%. Resistance variants (< 1%) were observed at most sites associated with DAA resistance from all classes, with the exception of sofosbuvir. **CONCLUSIONS:** Dominant resistant mutations were uncommonly observed in the setting of recent HCV. However, low level mutations to all DAA classes were observed by deep sequencing at the majority of sites, and in most individuals. The significance of these variants and impact on future treatment options remains to be determined.


**OBJECTIVE:** The effects of hepatitis C virus (HCV) coinfection on immune homeostasis and immune restoration in treated HIV infection are not well understood. **METHODS:** We studied 79 HIV-infected patients who had been receiving HAART for more than 2 years and who had HIV viral load below 50 copies/ml. Four patient groups were studied: HIV/HCV, CD4 cells above 350/μl; HIV/HCV, CD4 cells below 350/μl; HIV/HCV, CD4 cells above 350/μl; HIV/HCV, CD4 cells below 350/μl. Controls comprised 20 healthy volunteers. Naive, central memory, effector memory, and terminal effector CD4+ T cells were enumerated. Naive CD4CD31 T cells were counted as recent thymic emigrants (RTEs). Activation state and ex-vivo apoptosis of CD4 T cells, levels of liver enzymes, and aspartate aminotransferase-to-platelet ratio index were evaluated. **RESULTS:** CD4 T-cell counts and the numbers of all circulating CD4 T-cell maturation subsets were diminished in HIV infection; CD4 T-cell activation and apoptosis were increased in HIV infection, but none of these indices was affected by HCV coinfection. RTE numbers were diminished in HIV infection, were inversely related to age, and were increased in women and lower in HIV/HCV patients than in singly HIV-infected patients. In coinfected patients, RTE numbers were inversely related to levels of liver enzymes, but not to HCV viral load. **CONCLUSION:** Whereas we could find no relationship between HCV infection and most indices of CD4 T-cell homeostasis or activation, CD4 RTEs are diminished in the circulation of HCV coinfected persons and appear to be related to indices of ongoing hepatic damage or inflammation.


*Caring Ambassadors Program Hepatitis C Literature Review © 2014*
**BACKGROUND:** Faldaprevir is a potent, once-daily hepatitis C virus (HCV) NS3/4A protease inhibitor. Studies were performed to investigate potential drug interactions between faldaprevir and commonly used antiretrovirals darunavir/ritonavir, efavirenz and tenofovir to guide the co-administration of faldaprevir with these agents in HIV/HCV co-infected patients. **METHODS:** In three open-label, phase I pharmacokinetic (PK) studies, healthy adult volunteers received: (i) darunavir/ritonavir (800 mg/100 mg once daily [QD]) with and without faldaprevir (240 mg QD); (ii) faldaprevir (240 mg twice daily [BID]) with and without efavirenz (600 mg QD); or (iii) faldaprevir (240 mg BID) or tenofovir (300 mg QD) alone and in combination. To assess potential drug interactions, geometric mean ratios and 90% confidence intervals for PK parameters were calculated. Safety was evaluated. **RESULTS:** Efavirenz decreased faldaprevir AUC by 35%, Cmax by 28%, and Cmin by 46%, consistent with induction of CYP3A by efavirenz. Tenofovir decreased faldaprevir AUC by 22%, which was not considered clinically relevant. Faldaprevir had no clinically relevant effects on darunavir or tenofovir PK (15% and 22% AUC increase, respectively). Adverse events were consistent with the known safety profiles of faldaprevir and the antiretrovirals being examined. **CONCLUSIONS:** No clinically significant interactions were observed between faldaprevir and darunavir/ritonavir or tenofovir. A potentially clinically relevant decrease in faldaprevir exposure was observed when co-administered with efavirenz; this decrease can be managed using the higher of the two faldaprevir doses tested in phase III trials (240 mg QD as opposed to 120 mg QD).

---

**COMPLEMENTARY AND ALTERNATIVE MEDICINE**


Investigation of the alkaloids from Myrioneuron faberi, a plant unique to China, gave four pairs of enantiomers (1-4). (±)-β-Myrifabral A (1) and (±)-α-myrifabral A (2) formed an inseparable mixture of anomers (cluster A), as did (±)-β-myrifabral B (3) and (±)-α-myrifabral B (4) (cluster B). Their structures were determined by X-ray diffraction and NMR analysis. Compounds 1-4 possessed novel cyclohexane-fused octahydroquinolizine skeletons and represent the first quinolizidine alkaloids from the genus Myrioneuron. The epimers of cluster A (1 and 2) were modified and separated. In vitro, clusters A and B and their derivatives inhibited replication of hepatitis C virus (HCV, IC50 0.9 to 4.7 μM) with cytotoxicity lower than that of telaprevir.

**EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS**


**BACKGROUND:** A key aim of the Hepatitis C Action Plan for Scotland was to reduce the undiagnosed population through awareness-raising activities, for general practitioners and those at risk, and the introduction of dried blood spot (DBS) sampling in community drug services to overcome barriers to testing. This study evaluates the impact of these activities on testing and diagnosis. **METHODS:** Data on hepatitis C virus (HCV) testing undertaken between January 1999 and December 2011 in Scotland's four largest health boards were analysed. Segmented regression analysis was used to examine changes in testing following the (1) launch of the Action Plan and (2) introduction of DBS testing. **RESULTS:** Between the pre-Action Plan and Action Plan periods, increases were observed in the average number of HCV tests (19 058-29 045), positive tests (1993-2405) and new diagnoses (1221-1367). Since July 2009, 26% of new diagnoses were made in drug
services. The trend in the number of positive tests was raised during the Action Plan, compared to pre-Action Plan, particularly in drug services (rate ratio (RR)=1.4, p<0.001) and prisons (RR=1.2, p<0.001); no change was observed in general practice. Following introduction of DBS testing, there was a 3-fold increase in testing (RR=3.5, p<0.001) and 12-fold increase in positives (RR=12.1, p<0.001) in drug services. **CONCLUSIONS:** The introduction of DBS sampling in community drug services has made an appreciable contribution to efforts to diagnose the HCV-infected population in Scotland. These findings are important to other countries, with injecting-related HCV epidemics, needing to scale-up testing/case-finding initiatives.


**Introduction:** With the development of new highly efficacious direct acting antiviral treatments (DAAs) for hepatitis C (HCV), the concept of treatment as prevention is gaining credence. To date the majority of mathematical models assume perfect mixing with injectors having equal contact with all other injectors. This paper explores how using a networks based approach to treat people who inject drugs (PWID) with DAAs affects HCV prevalence. **Method:** Using observational data we parameterized an Exponential Random Graph Model containing 524 nodes. We simulated transmission of HCV through this network using a discrete time, stochastic transmission model. The effect of five treatment strategies on the prevalence of HCV was investigated; two of these strategies were 1) treat randomly selected nodes and 2) "treat your friends" where an individual is chosen at random for treatment and all their infected neighbours are treated. **Results:** As treatment coverage increases, HCV prevalence at 10 years reduces for both the high efficacy and low efficacy treatment. Within each set of parameters, the "treat your friends" strategy performed better than the random strategy being most marked for higher efficacy treatment. For example over 10 years of treating 25 per 1000 PWID, the prevalence drops from 50% to 40% for the random strategy, and to 33% for the "treat your friends" strategy (6.5% difference, 95% CI 5.1 - 8.1%). **Discussion:** "Treat your friends" is a feasible means of utilising network strategies to improve treatment efficiency. In an era of highly efficacious and highly tolerable treatment such an approach will benefit not just the individual but the community more broadly by reducing the prevalence of HCV amongst PWID. (Hepatology 2014).


**BACKGROUND AND AIMS:** Various inflammatory cytokines and adipokines have been implicated in HCV-mediated liver disease, and interleukin-6 (IL-6) and adiponectin may play key roles. In addition, these factors may be associated with chronic hepatitis C (CHC)-induced extrahepatic manifestations. However, little data are available on the role of these factors on future outcomes of CHC patients. **METHODS:** We evaluated the impact of serum levels of IL-6 and adiponectin on all-cause mortality, liver-related mortality, and liver-unrelated mortality, using a long-term follow-up study consisting of 325 CHC patients, for which we previously reported positive associations between these factors and hepatocellular carcinoma (HCC) development. **RESULTS:** During the follow-up period (mean, 13.0 yr), there were 92 events consisting of 91 deaths (liver-related, 72; liver-unrelated, 19) and 1 liver transplantation due to liver failure. High IL-6 and adiponectin levels, defined as being higher than each median value at baseline, were associated with significantly higher incidences of not only HCC development but also all-cause mortality. Interestingly, high IL-6 was strongly associated with only liver-related mortality, whereas high serum
adiponectin was associated with not only liver-related but also liver-unrelated mortality. Multivariate analysis identified high IL-6 as an independent risk factor for liver-related mortality and high adiponectin as an independent risk factor for liver-unrelated mortality. **CONCLUSIONS:** High serum levels of IL-6 and adiponectin were associated with higher all-cause and liver-related mortality in CHC patients. In addition, high adiponectin was associated with liver-unrelated mortality. The measurement of these factors may provide information useful for predicting future outcomes in CHC patients.


**INTRODUCTION:** Hepatitis C virus (HCV)-related arthritis is an uncommon disease belonging to the autoimmune disorders due to the chronic stimulus exerted by the virus on the immune system. It shows two clinical subsets: a symmetrical polyarthritis resembling rheumatoid arthritis but less aggressive and an intermittent mono-oligoarthritis involving the lower limbs. **AREAS COVERED:** We extensively review the current literature using the largest electronic databases (MEDLINE, EMBASE and COCHRANE) with regard to HCV-related arthritis (HCVrA) and studies focusing on the co-existence of HCV and other kinds of arthritides. **EXPERT OPINION:** The therapeutic approach to HCVrA remains largely empirical, because few studies have been published on this topic. Mainstream treatment based on the administration of hydroxychloroquine and low doses of corticosteroid is still largely preferred. Cyclosporine represents a useful alternative due to its antiviral properties. Anti-TNF agents are safe, but their hypothetic use appears excessive for a mild disorder such as HCVrA. IFN-α (and more recently pegylated IFN-α) when administered as a component of the combined (IFN-α + ribavirin) anti-HCV therapy can promote the appearance or the worsening of several autoimmune HCV-related disorders, including arthritis. New and forthcoming antiviral molecules will be used in the near future for a revolutionary IFN-free treatment.


Despite new Hepatitis C virus (HCV) therapeutic advances, challenges remain for HCV testing and linking patients to care. A point-of-care (POC) HCV antibody testing strategy was compared to traditional serological testing to determine patient preferences for type of testing and linkage to treatment in an innovative mobile medical clinic (MMC). From 2012 to 2013, all 1,345 MMC clients in New Haven, CT underwent a routine health assessment, including for HCV. Based on patient preferences, clients could select between standard phlebotomy or POC HCV testing, with results available in approximately 1 week versus 20 min, respectively. Outcomes included: (1) accepting HCV testing; (2) preference for rapid POC HCV testing; and (3) linkage to HCV care. All clients with reactive test results were referred to a HCV specialty clinic. Among the 438 (32.6 %) clients accepting HCV testing, HCV prevalence was 6.2 % (N = 27), and 209 (47.7 %) preferred POC testing. Significant correlates of accepting HCV testing was lower for the "baby boomer" generation (AOR 0.67; 95 % CI 0.46-0.97) and white race (AOR 0.55; 95 % CI 0.36-0.78) and higher for having had a prior STI diagnosis (AOR 5.03; 95 % CI 1.76-14.26), prior injection drug use (AOR 2.21; 95 % CI 1.12-4.46), and being US-born (AOR 1.76; 95 % CI 1.25-2.46). Those diagnosed with HCV and preferring POC testing (N = 16) were significantly more likely than those choosing standard testing (N = 11) to be linked to HCV care within 30 days (93.8 vs. 18.2 %; p < 0.0001). HCV testing is feasible in MMCs. While patients equally preferred POC and standard HCV testing strategies,
HCV-infected patients choosing POC testing were significantly more likely to be linked to HCV treatment. Important differences in risk and background were associated with type of HCV testing strategy selected. HCV testing strategies should be balanced based on costs, convenience, and ability to link to HCV treatment.

The changing burden of hepatitis C virus infection in the United States: model-based predictions.

BACKGROUND: Chronic hepatitis C virus (HCV) infection causes a substantial health and economic burden in the United States. With the availability of direct-acting antiviral agents, recently approved therapies and those under development, and 1-time birth-cohort screening, the burden of this disease is expected to decrease. OBJECTIVE: To predict the effect of new therapies and screening on chronic HCV infection and associated disease outcomes. DESIGN: Individual-level state-transition model. SETTING: Existing and anticipated therapies and screening for HCV infection in the United States. PATIENTS: Total HCV-infected population in the United States. MEASUREMENTS: The number of cases of chronic HCV infection and outcomes of advanced-stage HCV infection. RESULTS: The number of cases of chronic HCV infection decreased from 3.2 million in 2001 to 2.3 million in 2013. One-time birth-cohort screening beginning in 2013 is expected to identify 487,000 cases of HCV infection in the next 10 years. In contrast, 1-time universal screening could identify 933,700 cases. With the availability of highly effective therapies, HCV infection could become a rare disease in the next 22 years. Recently approved therapies for HCV infection and 1-time birth-cohort screening could prevent approximately 124,200 cases of decompensated cirrhosis, 78,800 cases of hepatocellular carcinoma, 126,500 liver-related deaths, and 9900 liver transplantations by 2050. Increasing the treatment capacity would further reduce the burden of HCV disease. LIMITATION: Institutionalized patients with HCV infection were excluded, and empirical data on the effectiveness of future therapies and on the future annual incidence and treatment capacity of HCV infection are lacking. CONCLUSION: New therapies for HCV infection and widespread implementation of screening and treatment will play an important role in reducing the burden of HCV disease. More aggressive screening recommendations are needed to identify a large pool of infected patients. PRIMARY FUNDING SOURCE: National Institutes of Health.

Modelling the impact of improving screening and treatment of chronic hepatitis C virus infection on future hepatocellular carcinoma rates and liver-related mortality.

BACKGROUND: The societal, clinical and economic burden imposed by the complications of chronic hepatitis C virus (HCV) infection - including cirrhosis and hepatocellular carcinoma (HCC) - is expected to increase over the coming decades. However, new therapies may improve sustained virological response (SVR) rates and shorten treatment duration. This study aimed to estimate the future burden of HCV-related disease in England if current management strategies remain the same and the impact of increasing diagnosis and treatment of HCV as new therapies become available.

METHODS: A previously published model was adapted for England using published literature and government reports, and validated through an iterative process of three meetings of HCV experts. The impact of increasing diagnosis and treatment of HCV as new therapies become available was modelled and compared to the base-case scenario of continuing current management strategies. To assess the 'best case' clinical benefit of new therapies, the number of patients treated was increased...
by a total of 115% by 2018. **RESULTS:** In the base-case scenario, total viraemic (HCV RNA-positive) cases of HCV in England will decrease from 144,000 in 2013 to 76,300 in 2030. However, due to the slow progression of chronic HCV, the number of individuals with cirrhosis, decompensated cirrhosis and HCC will continue to increase over this period. The model suggests that the 'best case' substantially reduces HCV-related hepatic disease and HCV-related liver mortality by 2020 compared to the base-case scenario. The number of HCV-related HCC cases would decrease 50% by 2020 and the number progressing from infection to decompensated cirrhosis would decline by 65%. Therefore, compared to projections of current practices, increasing treatment numbers by 115% by 2018 would reduce HCV-related mortality by 50% by 2020.

**CONCLUSIONS:**
This analysis suggests that with current treatment practices the number of patients developing HCV-related cirrhosis, decompensated cirrhosis and HCC will increase substantially, with HCV-related liver deaths likely to double by 2030. However, increasing diagnosis and treatment rates could optimise the reduction in the burden of disease produced by the new therapies, potentially halving HCV-related liver mortality and HCV-related HCC by 2020.


**BACKGROUND:** Chronic hepatitis C genotype 2 patients show high susceptibility to pegylated interferon plus ribavirin therapy (PEG/RBV). However, the differences in response to therapy between genotypes 2a and 2b, and the efficacy of prolonged therapy for refractory patients have not been evaluated. We investigated the differences in response to PEG/RBV between each genotype, and examined the efficacy of prolonged therapy. **METHODS:** A total of 343 chronic hepatitis patients infected with HCV genotype 2 (2a: n=195; 2b: n=148) were enrolled in this study. All patients received PEG/RBV for 24 (24 week group, n=242) or more weeks (prolonged group, n=101). We analyzed the differences in virological response between genotypes 2a and 2b. Clinical and virological factors of patients in the 24 week group and the prolonged treatment group were matched using propensity score analysis, and the efficacy of prolonged therapy established by comparing time of serum HCV disappearance for each genotype. **RESULTS:** Virological response tended to be higher for genotype 2a compared with genotype 2b; however, there was no significant difference in sustained virological response (SVR) rates between genotypes (2a: 78.3%; 2b: 70.2%; P=0.19). After propensity score matching, the adjusted P value for SVR rate was significantly different for genotype 2b patients with undetectable HCV RNA between weeks 5 and 8, and for genotype 2a patients with detectable HCV RNA at week 8. **CONCLUSION:** Prolonged therapy with PEG/RBV may be effective when serum HCV RNA is detectable at week 4 and week 8 for genotype 2b and 2a patients, respectively.

**Autophagy in HCV Infection: Keeping Fat and Inflammation at Bay.** Vescovo T1, Refolo G1, Romagnoli A, et al. Biomed Res Int. 2014;2014:265353. Epub 2014 Aug 5. Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease. Viral persistence and pathogenesis rely mainly on the ability of HCV to deregulate specific host processes, including lipid metabolism and innate immunity. Recently, autophagy has emerged as a cellular pathway, playing a role in several aspects of HCV infection. This review summarizes current knowledge on the molecular mechanisms that link the HCV life cycle with autophagy machinery. In particular, we discuss the role of HCV/autophagy interaction in dysregulating inflammation and lipid homeostasis and its potential for translational applications in the treatment of HCV-infected patients.

**BACKGROUND:** Even though hepatocytes are the main site for hepatitis C virus (HCV) replication, peripheral blood mononuclear cells (PBMC) have also been proposed as a suitable site for HCV replication. However, this issue still remains under discussion. We have previously developed an innovative system where HCV-RNA can be recovered during PBMC culture from HCV infected patients. Thus, the aim of this work was to use this novel approach in order to observe the evolution and replication of HCV genotype 1b in the PBMC of an HIV-HCV coinfected patient. **METHODS:** HCV-RNA was extracted from serum, uncultured PBMC and PBMC culture at day 6, 20 and 33. The evolutionary analysis was performed using the direct sequences of three viral regions: 5'UTR, E2 and NS5A. Additionally, E2 region was cloned in order to extend the evolutive analysis. **RESULTS:** In the present work, the molecular characterization of HCV along the culture showed a clear dynamic evolving process with the appearance of several nucleotide or amino acid changes in the three regions analyzed. Furthermore, the population analysis of E2 clones showed emerging and loss of lineages which indicate the fast evolutive dynamics of this system. **CONCLUSIONS:** Since evolution can take place only if the virus is replicating in the culture, this finding constitutes an important evidence of viral replication in PBMC. Moreover, this extrahepatic compartment could be very important due to the presence of distinctive variants that could be responsible for resistance to treatment, viral pathogenesis and other clinical implications.


On-treatment responses to antiviral therapy are used to determine duration of therapy in patients being treated for genotype 1 hepatitis C virus infection. Such use of response-guided therapy has successfully reduced exposure of patients to the side-effects of pegylated interferon and ribavirin without jeopardizing overall treatment success. Response-guided therapy is an integral part of treatment using the current standard treatments involving the direct-acting antiviral (DAA) agents--boceprevir or telaprevir--combined with pegylated interferon/ribavirin. Improvements in our understanding of the kinetics of viral load during antiviral therapy have shown us that more potent suppression of viral replication increases the rate of viral eradication, providing impetus for the development of more potent DAAs. Emerging results from clinical trials of these agents--including trials of interferon-free DAA combinations--suggest that very high rates of viral eradication are achievable, even in patients who failed to respond to previous courses of interferon-based therapy. Furthermore, because of these high rates of treatment success, on-treatment assessment of viral response may become unnecessary. The field of hepatitis C virus therapy is evolving rapidly and current trends indicate that the era of simple treatment regimens with high rates of success and good tolerability are near.

**LIVER CANCER**


Hepatitis C virus (HCV)-related cirrhosis represents the leading cause of liver transplantation in developed, Western and Eastern countries. Unfortunately, liver transplantation does not cure recipient HCV infection: reinfection universally occurs and disease progression is faster after liver transplant. In this review we focus on what happens throughout the peri-transplant phase and in the...
first 6-12 mo after transplantation: during this crucial period a completely new balance between HCV, liver graft, the recipient's immune response and anti-rejection therapy is achieved that will deeply affect subsequent outcomes. Nearly all patients show an early graft reinfection, with HCV viremia reaching and exceeding pre-transplant levels; in this setting, histological assessment is essential to differentiate recurrent hepatitis C from acute or chronic rejection; however, differentiating the two patterns remains difficult. The host immune response (mainly cellular mediated) appears to be crucial both in the control of HCV infection and in the genesis of rejection, and it is also strongly influenced by immunosuppressive treatment. At present no clear immunosuppressive strategy could be strongly recommended in HCV-positive recipients to prevent HCV recurrence, even immunotherapy appears to be ineffective. Nonetheless it seems reasonable that episodes of rejection and over-immunosuppression are more likely to enhance the risk of HCV recurrence through immunological mechanisms. Both complete prevention of rejection and optimization of immunosuppression should represent the main goals towards reducing the rate of graft HCV reinfection. In conclusion, post-transplant HCV recurrence remains an unresolved, thorny problem because many factors remain obscure and need to be better determined.


BACKGROUND: & Aims: Non-alcoholic fatty liver disease (NAFLD) is a risk factor for hepatocellular carcinoma (HCC). However, no systemic studies from the United States have examined temporal trends, HCC surveillance practices, and outcomes of NAFLD-related HCC. METHODS: We identified a national cohort of 1500 patients who developed HCC from 2005 through 2010 from Veterans Administration (VA) hospitals. We reviewed patients' full VA medical records; NAFLD was diagnosed based on histologic evidence for, or the presence of, metabolic syndrome in the absence of hepatitis C virus (HCV) infection, hepatitis B, or alcoholic liver disease. We compared annual prevalence values for the main risk factors (NAFLD, alcohol abuse, HCV), as well HCC surveillance and outcomes, among HCC patients. RESULTS: NAFLD was the underlying risk factor for HCC in 120 patients (8.0%); the annual proportion of NAFLD-related HCC remained relatively stable (7.5%-12.0%). In contrast, the proportion of HCC cases associated with HCV increased from 61.0% in 2005 (95% confidence interval, 53.1%-68.9%) to 74.9% in 2010 (95% confidence interval, 69.0%-80.7%). The proportion of HCC cases associated with only alcohol abuse decreased from 21.9% in 2005 to 15.7% in 2010, and the annual proportion of HCC cases associated with hepatitis B remained relatively stable (1.4%-3.5%). A significantly lower proportion of patients with NAFLD-related HCC had cirrhosis (58.3%) compared to patients with alcohol- or HCV-related HCC (72.4% and 85.6%, respectively; P<.05). A significantly higher percentage of patients with NAFLD-related HCC did not receive HCC surveillance in the 3 years before their HCC diagnosis, compared to patients with alcohol- or HCV-associated HCC. A lower proportion of patients with NAFLD-related HCC received HCC-specific treatment (61.5%) than of patients with HCV-related HCC (77.5%; P<.01). However, 1-year survival did not differ among patients with HCC related to different risk factors. CONCLUSIONS: NAFLD is the third most common risk factor for HCC in the VA. The proportion of NAFLD-related HCC was relatively stable from 2005 through 2010. Although patients with NAFLD-related HCC receive less HCC surveillance and treatment, a similar proportion survive for 1 year, compared to patients with alcohol- or HCV-related HCC.
Effect of Peginterferon alfa-2b and Ribavirin on Hepatocellular Carcinoma Prevention in Older Patients with Chronic Hepatitis C.


BACKGROUND & AIMS: The population of patients chronically infected with hepatitis C virus (HCV) is aging and the number of older patients with HCV-related hepatocellular carcinoma (HCC) is increasing. The purpose of this study was to elucidate the effects of peginterferon and ribavirin combination therapy on prevention of HCC in older patients with chronic hepatitis C (CH-C).

METHODS: We compared the sustained virological response (SVR) and treatment discontinuation rates between older (≥ 65 years) and younger patients (< 65 years) among 1280 CH-C patients treated with peginterferon alfa-2b and ribavirin. Cumulative incidence of HCC was determined by Kaplan-Meier analysis and factors associated with liver carcinogenesis were analyzed by Cox proportional hazards regression.

RESULTS: Older patients had a significantly lower SVR rate and a significantly higher discontinuation rate of treatment than younger patients. Fifty patients developed HCC during median follow-up period of 47 months. Cox proportional hazards regression analysis indicated that the following were independent risk factors associated with the development of HCC: older age, male, advanced fibrosis, Non-SVR in all patients: higher gamma-glutamyltranspeptidase (GGT), Non-SVR in older patients. Older patients who achieved SVR had a significantly reduced rate of HCC compared with those who did not achieve SVR, especially those who had GGT over 44IU/L.

CONCLUSIONS: The SVR rate was lower and the combination therapy discontinuation rate was higher in older CH-C patients than in younger patients. However, older patients who achieved SVR had a markedly lower rate of HCC development compared to older patients who did not achieve SVR.