
BACKGROUND: This large prospective multicentre cohort study aimed to improve knowledge of therapy for chronic hepatitis C (CHC) in real clinical practice. METHODS: A diverse population of adults with CHC including patients with comorbid conditions, laboratory abnormalities and demographic features [comorbidities or special populations (CSP)] who were under-represented or excluded from peginterferon registration studies was treated with peginterferon α-2a (40 kDa) or α-2b (12 kDa) plus ribavirin at the investigator's discretion.

RESULTS: During the study, 5399 treatment-naive patients [2527 (46.8%) with CSP] received peginterferon α-2a (n=3513, 65.1%) or peginterferon α-2b (n=1886, 34.9%). The sustained virological response rate was 56.6% (3057/5399) overall, 59.7% (1716/2872) in patients without CSP and 53.1% (1341/2527) in patients with CSP. Significant predictors of sustained virological response included hepatitis C virus genotype 2 or 3 infection, absence of cirrhosis, hepatitis C virus RNA ≤500 000 IU/ml, alanine transaminase quotient >3× the upper limit of normal, age ≤65 years, BMI <25 kg/m², at least 80% of the planned exposure to peginterferon and ribavirin and prescription of peginterferon α-2a.

CONCLUSION: The results provide detailed information on the outcome of therapy for CHC in a diverse Italian population that included a large number of patients with CSP and provides an insight into the generalizability of the results obtained in the more restricted setting of randomized registration trials.


Introduction: Hepatitis C virus (HCV) therapy continues to evolve rapidly. ABT-450 is a novel potent inhibitor of the non-structural 3/4A protease that has been studied in combination with several agents, allowing shorter duration of therapy and interferon-free/ribavirin-free all-oral regimens. Preliminary data from studies evaluating these new regimens are impressive with sustained virological response (SVR) rates of 88 - 100% after 12 weeks of therapy in patients
with previously untreated HCV genotype 1 infection. SVR rates in treatment-experienced patients are also encouraging. Areas covered: Efficacy and tolerability of antiviral regimens containing ABT-450 boosted with ritonavir (ABT-450/r). Results from published studies and abstracts from recent meetings are presented. Expert opinion: Newer direct-acting antiviral agents such as ABT-450 promise effective and durable suppression of HCV with interferon/ribavirin-free all-oral regimens. This agent also allows for shorter duration of treatment and has tolerable side effects. Results of clinical trials including a broader spectrum of individuals with HCV infection are eagerly awaited.


Hepatitis C virus (HCV) is mainly transmitted by parenteral route, being blood transfusion and intravenous drug use the most frequent risk factors. However, it has been suggested that there are other routes of transmission. There are several studies where HCV RNA has been detected in saliva of patients infected with HCV, and epidemiological studies have proposed the dental treatments as possible risk factors for HCV transmission. The purpose of this study was to detect the presence of HCV RNA in saliva of patients with active infection and associating with periodontal or liver disease. METHODS: Patients with quantifiable HCV-RNA in serum were enrolled in the study. Periodontal disease was assessed using the modified gingival index (MGI). Presence of dental plaque was assessed with the use of disclosing tablets. Patients were clinically and laboratory evaluated to identify the stage of liver disease, the HCV RNA was determinate in saliva by nested RT-PCR. To determine associations between different parameters univariate and multivariate analysis were used. RESULTS: A total of 45 patients were included. Of these patients, 21 (46.6%) had hepatitis, 23 (51.1%) had cirrhosis and one patient (2.4%) presented hepatocellular carcinoma (HCC). Viral loads in serum ranged from 2.31-6.68 log IU/ml with a mean of 5.46 log IU/ml (95% CI 5.23-5.70). HCV RNA was positive in saliva of 29 patients (64.4%) and was not detected in 16 (35.6%). For univariate analysis three independent variables were associated with the detection of HCV-RNA in saliva: gender, viral load and dental plaque and multivariate analysis only one independent variable viral load >5.17 log IU/mL remained significantly associated with the detection of HCV in saliva (p = 0.0002). A statistical difference was observed when viral load was analyzed, log 5.85 IU/mL (95% CI 5.67-6.02) for patients with HCV in saliva vs. log 4.77 IU/mL (95% CI 4.35-5.19) for patients without HCV in saliva (p = 0.0001). The detection of HCV-RNA in saliva was more frequent in patients with relatively high serum viral loads. CONCLUSION: HCV-RNA in saliva was associated with the level of serum viral load but not with periodontal or liver disease severity.


Hepatitis C virus (HCV)-related cryoglobulinemia commonly causes disabling complications including peripheral neuropathy and neuropathic pain. In this prospective clinical, neurophysiological, and skin biopsy study we aimed at assessing clinical characteristics and risk factors of peripheral neuropathy and neuropathic pain in patients with HCV-related
cryoglobulinemia. We enrolled 69 consecutive patients with HCV-related cryoglobulinemia. We
diagnosed neuropathic pain with the DN4 (Neuropathic Pain Diagnostic) questionnaire, and rated
the various neuropathic pains with the Neuropathic Pain Symptom Inventory (NPSI). All patients
underwent a standard nerve conduction study to assess Aδ-fiber function, laser-evoked potentials
to assess Aβ-fiber function, and skin biopsy to assess C-fiber terminals. Of the 69 patients
studied, 47 had a peripheral neuropathy, and 29 had neuropathic pain. Patients with peripheral
neuropathy were older than those without (P < 0.0001). While peripheral neuropathy was
significantly associated with the duration of HCV infection (P < 0.01), it was unrelated to the
duration of cryoglobulinemia and cryocrit (P > 0.5). The severity of peripheral neuropathy
significantly correlated with the duration of HCV infection (P < 0.05). Laser-evoked potential
amplitudes were significantly lower in patients with than in those without neuropathic pain (P <
0.05). Conversely, no difference was found in nerve conduction study and skin biopsy findings
(P > 0.05). Our findings show that peripheral neuropathy is related to age and HCV infection,
rather than to cryoglobulinemia, and neuropathic pain is associated with damage to nociceptive
pathways as assessed with laser-evoked potentials; this might be useful for designing more
effective clinical interventions for these common HCV related-cryoglobulinemia complications.

Baseline Comorbidities Enhance the Risk of Treatment-Induced Depression in HCV-
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Background. Hepatitis C virus (HCV) infection is associated with clinical depression, a
condition that is aggravated on interferon-based therapy. In HCV infection, men often appear
more resilient to depression than women. However, men are subject to depression in diseases
that tend to be comorbid in HCV-infected. Aim. This study examined whether HCV-infected
men with baseline comorbidities were more or less susceptible to depression prior to and on
treatment. Methods. Patients with chronic HCV infection preparing to begin treatment
participated (n = 37). The presence of baseline comorbidities was determined by pretreatment
medication regimes. Depression was measured by the Beck Depression Inventory prior to and
following 2, 4, 8, and 12 weeks of interferon therapy. Results. At baseline, cohorts with (n = 16)
and without (n = 21) comorbidities had equivocal demographics and infection characteristics.
Comorbidities did not associate with baseline depression. However, on treatment, men with
baseline comorbidities demonstrated an elevated risk for the onset of de novo depression (odds
ratio = 19.25; confidence interval = 1.41, 582.14; p = .008). This was not observed for women.
Baseline comorbidities did not alter the need for treatment discontinuations or the ability to
achieve a sustained viral response. Conclusion. The results of this study suggest that baseline
comorbidities render men more susceptible to interferon treatment-induced depression.

Treatment of chronic viral hepatitis C in children and adolescents: UK experience. Abdel-
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AIM: To review the efficacy and tolerability of pegylated interferon-α and ribavirin for
treatment of chronic hepatitis C (CHC) in children in the UK. METHODS: Retrospective
review of children treated for CHC in 3 UK paediatric specialist liver centres between 2005 and
2010. Data on viral response to treatment, demographic and clinical details were collected.
Treatment outcome was assessed by the absence of detectable viral RNA in blood 24 weeks after treatment-sustained viral response (SVR). 

**RESULTS:** 75 children were included; 34 genotype 1; 39 genotypes 2 and 3; 2 genotype 4. Overall SVR was achieved in 54/71 (76%); 65% genotype 1; 89% genotypes 2 and 3; 100% genotype 4. Early response at 12 weeks was achieved in 53 and sustained in 47 (89%). Data on rapid response after 4 weeks of treatment were available in 25: 17/25 (68%) responded and 16 of these (94%) achieved SVR. IL28 T/T genotype was associated with higher SVR. There were no significant changes in weight and height z scores from baseline compared with 24 weeks post-treatment follow-up. No child discontinued treatment due to side effects, although 43 required dose modification. Treatment affected quality of life (QoL) in the initial 12 weeks of treatment, which improved by the end of treatment. 

**CONCLUSIONS:** Children respond well to therapy for CHC. Treatment was tolerated with minimal impact on QoL and no significant effect on growth. Knowledge of viral and IL28 genotypes and early viral response is useful to plan treatment in children and provide appropriate counselling.


**BACKGROUND:** Hepatitis C virus infection (HCV) has a significant global health burden with an estimated 2%-3% of the world's population infected, and more than 350,000 dying annually from HCV-related conditions including liver failure and liver cancer. Prisons potentially offer a relatively stable environment in which to commence treatment as they usually provide good access to health care providers, and are organised around routine and structure. Uptake of treatment of HCV, however, remains low in the community and in prisons. In this study, we explored factors affecting treatment uptake inside prisons and hypothesised that prisoners have unique issues influencing HCV treatment uptake as a consequence of their incarceration which are not experienced in other populations. 

**METHOD AND FINDINGS:** We undertook a qualitative study exploring prisoners' accounts of why they refused, deferred, delayed or discontinued HCV treatment in prison. Between 2010 and 2013, 116 Australian inmates were interviewed from prisons in New South Wales, Queensland, and Western Australia. Prisoners experienced many factors similar to those which influence treatment uptake of those living with HCV infection in the community. Incarceration, however, provides different circumstances of how these factors are experienced which need to be better understood if the number of prisoners receiving treatment is to be increased. We developed a descriptive model of patient readiness and motivators for HCV treatment inside prisons and discussed how we can improve treatment uptake among prisoners. 

**CONCLUSION:** This study identified a broad and unique range of challenges to treatment of HCV in prison. Some of these are likely to be diminished by improving treatment options and improved models of health care delivery. Other barriers relate to inmate understanding of their illness and stigmatisation by other inmates and custodial staff and generally appear less amenable to change although there is potential for peer-based education to address lack of knowledge and stigma.

BACKGROUND: HCV is a major cause of chronic liver disease in Egypt. AIMS: is to study the prevalence of photosensitivity among asymptomatic HCV infected patients and its possible relation to porphyrins levels and whether it can be considered an alarm for early diagnosis of the disease which is the most important goal in the management. METHODS: The study included 100 accidentally discovered HCV positive cases and 100 HCV negative healthy controls. All patients and controls were subjected to: Detailed history and clinical examination, dermatological examination including evaluation of reaction to solar exposure, measurement of serum AST, ALT, albumin, bilirubin, serum and urinary porphyrins levels. RESULTS: The prevalence of photosensitivity among HCV positive cases (33%) was significantly higher compared to 10% in the control group. Serum porphyrins were positive in 46 cases (46%), twenty three cases (23%) had positive urinary porphyrins, while only four controls (4%) showed positive serum porphyrins and one (1%) showed positive urinary porphyrins, the difference was statistically significant. Cases with photosensitivity showed significantly higher prevalence of serum and urinary porphyrins existence as well as serum porphyrins levels. Levels of viraemia showed statistically significant relation to levels of porphyrins. CONCLUSION: Asymptomatic chronic HCV infection cases showed significantly high prevalence of photosensitivity which is related to the associated disturbance of porphyrins metabolism. Photosensitivity can thus be considered an early marker of HCV infection. Patients discovered to have recently acquired photosensitivity should be screened for HCV infection especially in endemic areas like Egypt.


BACKGROUND: Different parameters have been determined for prediction of treatment outcome in hepatitis c virus genotype 1 infected patients undergoing pegylated interferon, ribavirin combination therapy. Results on the importance of vitamin D levels are conflicting. In the present study, a comprehensive analysis of vitamin D levels before and during therapy together with single nucleotide polymorphisms involved in vitamin D metabolism in the context of other known treatment predictors has been performed. METHODS: In a well characterized prospective cohort of 398 genotype 1 infected patients treated with pegylated interferon-α and ribavirin for 24-72 weeks (INDIV-2 study) 25-OH-vitamin D levels and different single nucleotide polymorphisms were analyzed together with known biochemical parameters for a correlation with virologic treatment outcome. RESULTS: Fluctuations of more than 5 (10) ng/ml in 25-OH-vitamin D-levels have been observed in 66 (39) % of patients during the course of antiviral therapy and neither pretreatment nor under treatment 25-OH-vitamin D-levels were associated with treatment outcome. The DHCR7-TT-polymorphism within the 7-dehydrocholesterol-reductase showed a significant association (P=0.031) to sustained viral response in univariate analysis. Among numerous further parameters analyzed we found that age (OR=1.028, CI=1.002-1.056, P=0.035), cholesterol (OR=0.983, CI=0.975-0.991, P<0.001), ferritin (OR=1.002, CI=1.000-1.004, P=0.033), gGT (OR=1.467, CI=1.073-2.006, P=0.016) and IL28B-genotype (OR=2.442, CI=1.271-4.695, P=0.007) constituted the strongest predictors of treatment response. CONCLUSIONS: While 25-OH-vitamin D-levels levels show considerable variations during the long-lasting course of antiviral therapy they do not show any significant association to treatment outcome in genotype 1 infected patients.

**BACKGROUND:** Plasma and hepatic lipid abnormalities are frequent in hepatitis C infected individuals. **METHODS:** Plasma lipid and medical records profiles were prospectively obtained in 130 consecutive individuals seen by a single hepatologist in a university liver disease clinic. The relationships between viral load, genotype, plasma lipid fractions, HDL, LDL particle number and particle size were examined. **RESULTS:** Of 130 individuals studied, 74 had hepatitis C while 15 had NAFLD/NASH and 30 had alcohol related liver disease. The LDL particle number and LDL-C levels did not differ between those with and without hepatitis C although the number of small LDL particles was greater in those with hepatitis C infection. The HDL-C and total cholesterol levels were greater in those without hepatitis C than those with hepatitis C (P = 0.009). In contrast, the serum triglyceride level was greater in the hepatitis C viral group (P = 0.013). Importantly, the hepatitis C viral load regardless of the genotype correlated directly with the triglyceride and VLDL levels with r values of 0.73 and 0.84, respectively. **CONCLUSIONS:** There are: (1) important differences in lipid classes, number and the size of lipid particles exist between hepatitis C virus infected and noninfected liver disease groups, (2) the serum total triglyceride and the LDL levels correlate significantly with the hepatitis C viral load and, (3) Serum triglyceride level may play an important role in viral replication. These data further suggest that therapies directed at lowering plasma triglyceride levels may enhance the efficacy of current antiviral treatment regimens.


**Background:** Opiate substitution therapy (OST) reduces the risk of death from directly drug-related causes in heroin users, allowing other chronic health problems to emerge. People who inject drugs (PWID) are exposed to hepatitis C virus (HCV), with an associated risk of chronic liver disease. We investigated HCV prevalence and liver-related morbidity in a cohort of OST recipients, and analyzed factors associated with significant hepatic fibrosis. **Methods:** All patients registered on 1 April 2008 in 4 clinics providing OST in the 3 largest cities in Sweden were eligible for inclusion. HCV viremic subjects were evaluated for fibrosis stage by liver biopsy, transient elastometry (TE), and/or a biochemical fibrosis index (Göteborg University Cirrhosis Index; GUCI). Factors associated with severity of fibrosis were determined by logistic regression analysis. **Results:** Out of 524 eligible patients, 277 consented to enrolment. Two hundred and thirty-six subjects (88%) were anti-HCV-positive, and 162 of these were viremic (69%). Significant liver fibrosis (defined as Ishak stages F3-F6, TE value ≥ 8.85 kPa, or GUCI > 0.33) was found in 69 out of 103 (67%) tested viremic patients, and was associated with alcohol intake (p = 0.03), higher body mass index (BMI; p = 0.04), and the presence of anti-HBc antibodies (indicating exposure to hepatitis B virus (HBV); p = 0.02). **Conclusions:** Significant liver fibrosis was detected in two-thirds of HCV viremic OST recipients in this cohort, and was associated with alcohol use, high BMI, and exposure to HBV. These findings indicate that the management of HCV and associated risk factors should be emphasized in Swedish OST programs.
The efficacy and safety of treating hepatitis C in patients with a diagnosis of schizophrenia.

Treating chronic hepatitis C with pegylated interferon alpha may induce or exacerbate psychiatric illness including depression, mania and aggressive behaviour. There is limited data regarding treatment in the context of chronic schizophrenia. We sought to establish the safety and efficacy of treating patients with schizophrenia. Patient and treatment data, prospectively collected on the Scottish hepatitis C database, were analysed according to the presence or absence of a diagnosis of schizophrenia. Time from referral to treatment, and the proportion of patients commencing treatment in each group, was calculated. Outcomes including sustained viral response rates, reasons for treatment termination and adverse events were compared. Of 5497 patients, 64 (1.2%) had a diagnosis of schizophrenia. Patients with schizophrenia (PWS) were as likely to receive treatment as those without [28/61(46%) vs 1639/4415 (37%) P = 0.19]. Sustained viral response (SVR) rates were higher in PWS [21/25 (84%) vs 788/1453 (54%) P < 0.01]. SVR rates by genotype were similar [4/8 (50%) vs 239/684 (35%) Genotype 1 (P = 0.56), 17/17 (100%) vs 599/742 (81%) non-Genotype 1 (P = 0.09)]. Adverse events leading to cessation of treatment were comparable [2/25(8%) vs 189/1453 (13%) P: 0.66]. Patients with schizophrenia are good candidates for hepatitis C treatment, with equivalent SVR and treatment discontinuation rates to patients without schizophrenia.


AIM: To determine the frequencies of mutations that cause inherited monogenic liver disorders in patients with chronic hepatitis C. METHODS: This study included 86 patients with chronic hepatitis C (55 men, 31 women; mean age at diagnosis, 38.36 ± 14.52 years) who had undergone antiviral therapy comprising pegylated interferon and ribavirin. Viral load, biochemical parameter changes, and liver biopsy morphological data were evaluated in all patients. The control group comprised 271 unrelated individuals representing the general population of Latvia for mutation frequency calculations. The most frequent mutations that cause inherited liver disorders [gene (mutation): ATP7B (H1069Q), HFE (C282Y, H63D), UGT1A1 (TA)7, and SERPINA1 (PiZ)] were detected by polymerase chain reaction (PCR), bidirectional PCR allele-specific amplification, restriction fragment length polymorphism analysis, and sequencing. RESULTS: The viral genotype was detected in 80 of the 86 patients. Viral genotypes 1, 2, and 3 were present in 61 (76%), 7 (9%), and 12 (15%) patients, respectively. Among all 86 patients, 50 (58%) reached an early viral response and 70 (81%) reached a sustained viral response. All 16 patients who did not reach a sustained viral response had viral genotype 1. Case-control analysis revealed a statistically significant difference in only the H1069Q mutation between patients and controls (patients, 0.057; controls, 0.012; odds ratio, 5.514; 95%CI: 1.119-29.827, P = 0.022). However, the H1069Q mutation was not associated with antiviral treatment outcomes or biochemical indices. The (TA) 7 mutation of the UGT1A1 gene was associated with decreased ferritin levels (beta regression coefficient = -295.7, P = 0.0087). CONCLUSION: Genetic mutations that cause inherited liver diseases in patients with hepatitis C should be studied in detail.

It is well known that chronic hepatitis C is associated with insulin resistance and metabolic syndrome which are risk factors for atherosclerosis and coronary heart disease. As a result, chronic hepatitis C might be thought, through its association with metabolic syndrome, to increase the risk of myocardial infarction. However, unexpectedly it was found that HCV infection is not associated with an increased risk of myocardial infarction. We are providing here an hypothesis of the mechanism through which HCV infection does not increase the risk for myocardial infarction and also may be protecting against some cardiovascular risks that typically develop in many patients with metabolic syndrome who do not have chronic hepatitis C. The suggested mechanism includes factors that are normal consequences of chronic hepatitis, such as: significant decrease in cholesterol and LDL levels; defected blood clotting system; impaired myocardial function; decreased venous return and central venous pressure; increased nitric oxide and TNF alpha levels; and diminished cardiac beta receptors signal transduction. All these factors contribute to a protective effect against cardiac ischemia and coronary heart disease. We suggest further studies to investigate this hypothesis.


Characterization of antibodies targeting the attachment and entry of the viral particles into host cells is important for studying antibody mediated neutralization. Antibodies against the envelope glycoproteins (EGP) have neutralizing capacity and can prevent HCV infections. System based on HCV pseudo typed-particles (HCVpp) stably expressing EGP can be used for screening of HCV anti envelope neutralizing antibodies in the serum of patients with acute and chronic HCV infections. The aim of the current study was to check HCVpp as a useful tool for the detection of anti-HCV envelope antibodies in the serum of HCV infected patients and to test the binding potential of these antiviral molecules to EGP of HCV 3a. Previously developed HCVpp harboring unmodified glycoproteins from local isolates in 293T cell line were used in this study. HCVpp were pre incubated with different concentrations of anti E1 antibody and different E2 antibodies to check antiviral activity. Further we used serum samples with low/medium (<800,000 IU/mL), and high (>800,000 IU/mL) viral titer from chronic HCV male and female patients. Infection was done in Huh-7 cells for 1 h at 37 oC. Infectivity was checked through Luciferase assay. Considerable decrease in HCVpp infectivity with anti-envelope antibodies was observed in dose dependent manner. Maximum inhibition was seen when 5 µg/ml of monoclonal anti E1 antibody used. Further increase in concentration exhibited no decrease in infectivity which suggests that other factors are also involved in causing infection. Various well characterized E2-specific monoclonal antibodies (mAbs) have been screened for their capability to reduce infection in Huh-7 cells. Three of the four mAbs specific for the E2 had no effect on the infectivity of HCVpp. Confirmation sensitive antibody H53 showed maximum inhibition of infectivity. HCV ELISA positive samples from both male and female patients were used to
neutralize the HCVpp. The neutralizing antibody response was observed in both males and females patients and do not assemble the rapidly evolving HCV envelope glycoproteins. That is why in spite the presence of neutralizing antibodies in the blood they fail to resolve infections. Moreover E1 antibodies insignificantly (>0.05) inhibit HCVpp infectivity while E2 antibodies significantly (<0.05) inhibit HCVpp infection. Based on the results of this study it is concluded that anti-envelope antibodies particularly the anti-E2 could be extremely valuable for characterizing the humoral immune response to HCV and for evaluating the potential for developing passive and active immunization for hepatitis C along with interferon therapy.

Chronic hepatitis C virus (HCV) infection results in a progressive disease that may end in cirrhosis and, eventually, in hepatocellular carcinoma. In the last several years, tremendous progress has been made in understanding the HCV life cycle and in the development of small molecule compounds for the treatment of chronic hepatitis C. Nevertheless, the complete understanding of HCV assembly and particle release as well as the detailed characterization and structure of HCV particles is still missing. One of the most important events in the HCV assembly is the nucleocapsid formation which is driven by the core protein, that can oligomerize upon interaction with viral RNA, and is orchestrated by viral and host proteins. Despite a growing number of new factors involved in HCV assembly process, we do not know the three-dimensional structure of the core protein or its topology in the nucleocapsid. Since the core protein contains a hydrophobic C-terminal domain responsible for the binding to cellular membranes, the assembly pathway of HCV virions might proceed via coassembly at endoplasmic reticulum membranes. Recently, new mechanisms involving viral proteins and host factors in HCV particle formation and egress have been described. The present review aims to summarize the advances in our understanding of HCV assembly with an emphasis on the core protein as a structural component of virus particles that possesses the ability to interact with a variety of cellular components and is potentially an attractive target for the development of a novel class of anti-HCV agents.

OBJECTIVE: Hepatitis C virus (HCV) is associated with B cell lymphoproliferative disorders, including mixed cryoglobulinemia (MC) vasculitis and B cell non-Hodgkin's lymphoma. The expansion of clonal and autoreactive rheumatoid factor-bearing CD21(-/low) marginal zone (MZ) B cells was demonstrated in patients with HCV-associated MC vasculitis. Fc receptor-like (FCRL) proteins comprise a family of immunoregulatory proteins preferentially expressed on B lineage cells. The goal of this study was to investigate the expression of FCRL proteins 1-5 on B cells from patients with HCV-associated MC vasculitis. METHODS: Expression of FCRL proteins 1-5 was assessed by flow cytometry on B cells from 15 HCV-infected patients with type II MC (7 of whom had B cell non-Hodgkin's lymphoma), 20 HCV-infected patients without MC, and 20 healthy donors. To evaluate FCRL-5 as an immunotherapy target in HCV-associated MC
vasculitis, 2 anti-FCRL-5 recombinant immunotoxins were produced using anti-FCRL-5 monoclonal antibodies and Pseudomonas exotoxin. **RESULTS:** Expression of FCRLs 2, 3, and 5 was markedly increased while expression of FCRL-1 was decreased on clonal CD21(-/low) MZ B cells, as compared with other B cell subsets, from HCV-infected patients and healthy donors. However, there was no difference in the pattern of FCRL expression between HCV-MC patients with lymphoma and those without lymphoma. The anti-FCRL-5 immunotoxins showed specific cytotoxicity against FCRL-5-expressing clonal CD21(-/low) MZ B cells isolated from HCV-infected patients as well as FCRL-5-transfected cell lines. No cytotoxicity against T cells or conventional B cells was observed. **CONCLUSION:** These findings suggest that FCRL-5-targeting therapies could be a specific treatment for HCV-associated MC vasculitis and other FCRL-5-positive autoimmune B cell disorders.


NS2 protein is essential for hepatitis C virus (HCV) replication. NS2 protein was expressed and purified. Aptamers against NS2 protein were raised and antiviral effects of the aptamers were examined. The molecular mechanism through which the aptamers exert their anti-HCV activity was investigated. The data showed that aptamer NS2-3 inhibited HCV RNA replication in replicon cell line and infectious HCV cell culture system. NS2-3 and another aptamer NS2-2 were demonstrated to inhibit infectious virus production without cytotoxicity in vitro. They did not affect hepatitis B virus replication. Interferon beta (IFN-β) and interferon-stimulated genes (ISGs) were not induced by the aptamers in HCV-infected hepatocytes. Furthermore, our study showed that N-terminal region of NS2 protein is involved in the inhibition of HCV infection by NS2-2. I861T within NS2 is the major resistance mutation identified. Aptamer NS2-2 disrupts the interaction of NS2 with NS5A protein. The data suggest that NS2-2 aptamer against NS2 protein exerts its antiviral effects through binding to the N-terminal of NS2 and disrupting the interaction of NS2 with NS5A protein. NS2-specific aptamer is the first NS2 inhibitor and can be used to understand the mechanisms of virus replication and assembly. It may be served as attractive candidates for inclusion in the future HCV direct-acting antiviral combination therapies.


Hepatitis C virus (HCV) quasispecies constitute a dynamic population in a continuous process of variation and selection. To investigate effect of the immune system on the genetic variability of HCV, we compared the hypervariable region 1 (HVR1) of immunosuppressed patients with chronic renal failure (CRF group) to immunocompetent patients with HCV chronic infection (control group). The HVR1 from ten samples of each group was amplified, cloned and sequenced. The HCV quasispecies from the control group had a higher frequency of variable sites in HVR1 (83.9 % vs 59.3 %, p < 0.05), as well as a greater diversity within (intra-patient) and between samples, compared to the CRF group. The clustering of the majority of the quasispecies of the CRF group in the phylogenetic tree also showed the limited diversity of the
quasispecies in immunosuppressed patients. Moreover, a higher variability of amino acids at positions 384, 386, 391, 394, 397, 398, 400, 405 and 410 was observed in the control group than in the CRF group, which showed a greater variability only at position 388 (p < 0.05). These data corroborates the hypothesis that the major selective pressure factor is the immune system, which promotes a high degree of diversity in the viral progeny and contributes to a constant evolution of HCV.


Hepatitis C virus (HCV) infects 180 million people worldwide and is a leading cause of liver disease such as fibrosis, cirrhosis and hepatocellular carcinoma. It has been shown that HCV can spread to naïve cells using two distinct entry mechanisms, "cell-free" entry of infectious extracellular virions that have been released by infected cells and direct "cell-to-cell" transmission. Here, we examined host-cell requirements for HCV spread and found that the cholesterol uptake receptor NPC1L1, which we recently identified as being an antiviral target involved in HCV cell-free entry/spread, is also required for the cell-to-cell spread. In contrast, the VLDL pathway, which is required for the secretion of cell-free infectious virus and thus has been identified as antiviral target for blocking cell-free virus secretion/spread, is not required for cell-to-cell spread. Noting that HCV cell-free and cell-to-cell spread share some common factors but not others, we tested the therapeutic implications of these observations and demonstrate that inhibitors that target cell factors required for both forms of HCV spread exhibit synergy when used in combination with interferon (a representative inhibitor of intracellular HCV production), while inhibitors that block only cell-free spread do not. This provides insight into mechanistic basis of synergy between interferon and HCV entry inhibitors and highlights the broader, previously unappreciated impact blocking HCV cell-to-cell spread can have on the efficacy of HCV combination therapies. **IMPORTANCE STATEMENT:** HCV can spread to naïve cells using distinct mechanisms, "cell-free" entry of extracellular virus and direct "cell-to-cell" transmission. Herein, we identify the host cell HCV entry factor NPC1L1 as also being required for HCV cell-to-cell spread, while showing that the VLDL pathway, which is required for the secretion of cell-free infectious virus, is not required for cell-to-cell spread. While both these host factors are considered viable antiviral targets, we demonstrate that only inhibitors that block factors required for both forms of HCV entry/spread (i.e. NPC1L1) exhibit synergy when used in combination with interferon, while inhibitors that block factors only required for cell-free spread (i.e. VLDL pathway components) do not. Thus, this study advances our understanding of HCV cell-to-cell spread, provides mechanistic insight into the basis of drug synergy and highlights inhibition of HCV spread as a previously unappreciated consideration in HCV therapy design.


Oxidative stress and dysregulated cholesterol metabolism are characteristic features of chronic hepatitis C virus infection (CHC). Therefore, we analyzed serum oxysterol profiles in CHC patients and examined the significance of oxysterols in CHC. The concentrations of 7α-
hydroxycholesterol, 4β-hydroxycholesterol and 25-hydroxycholesterol as determined by LC-ESI-MS/MS were significantly elevated by +236%, +29% and +44%, respectively, in CHC patients compared with controls. Moreover, the elevated levels were significantly decreased by anti-viral therapy using PEGylated-interferon and ribavirin for 3 months. In contrast, 24S-hydroxycholesterol, 27-hydroxycholesterol and 7α-hydroxy-4-cholesten-3-one concentrations were not affected by CHC or anti-viral treatment. These results suggest that some oxysterols that are elevated in CHC are produced by cholesterol autoxidation due to oxidative stress or inflammation in the liver. Oxysterols may represent novel targets for the inhibition of disease progression and the prevention of hepatocarcinogenesis in CHC patients.


OBJECTIVES: The aim of this study was to determine the longitudinal effects of selective serotonin reuptake inhibitor (SSRI) therapy and cytokine-related depression on levels of hepatitis C virus (HCV) during treatment with combination therapy. BACKGROUND: Prior studies have investigated the association between cytokine-related depression and sustained virological response, but it is unknown whether anti-inflammatory properties of SSRIs used to treat cytokine-related depression inadvertently contravene proinflammatory properties of pegylated interferon (Peg-IFN), in effect reducing therapeutic efficacy. STUDY: In a retrospective cohort design, patients being treated with Peg-IFN or interferon in combination with ribavirin at a gastroenterology clinic were followed from initiation of therapy until 24 weeks after the completion of therapy. Sustained virological response and rate of decline of HCV RNA levels were compared among patients with SSRI therapy and cytokine-related depression. RESULTS: Selective serotonin reuptake inhibitor therapy and cytokine-related depression did not adversely impact the proportion of patients achieving sustained virological response. In a multivariate longitudinal analysis, the mean slope of HCV RNA levels declined faster over time in patients without cytokine-related depression in comparison to patients with cytokine-related depression (P = 0.05), and the mean slope of HCV RNA levels declined similarly over time in patients with and without SSRI therapy. CONCLUSIONS: In this retrospective cohort, SSRI therapy did not interfere with immune activation dynamics of Peg-IFN/ribavirin, and patients without cytokine-related depression developed quicker responses and suppressed HCV replication more favorably over time.


To assess differing patterns and levels of ascitic fluid cytokine and growth factors exist between those with a high risk and low risk of spontaneous bacterial peritonitis (SBP). METHODS: A total of 57 consecutive patients with ascites requiring a large volume paracentesis were studied. Their age, gender, specific underlying disease conditions were recorded after a review of their clinical records. Each underwent a routine assessment prior to their paracentesis consisting of a complete blood count, complete metabolic profile and prothrombin time/international normalized ratio (INR) determination. The ascitic fluid was cultured and a complete cell count and albumin
determination was obtained on the fluid. In addition, blood and ascitic fluid was assessed for the levels of interleukin interleukin (IL)-1A, IL-1B, IL-2, IL-4, IL-8, IL-10, monocyte chemotactic protein (MCP)-1, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) utilizing the Randox Biochip platforms (Boston, MA). A serum-ascites gradient, for each cytokine and growth factor was calculated. The results are reported as mean ± SEM between disease groups with statistical analysis consisting of the student t-test (two tailed) with a P value of 0.05 defining significance.

RESULTS: No clinically important demographic or biochemical differences between the 4 groups studied were evident. In contrast, marked difference in the cytokine and growth factors levels and pattern were evident between the 4 disease groups. Individuals with alcoholic cirrhosis had the highest levels of IL-1A, IL-1B, IL-4, IFNγ. Those with malignant disease had the highest levels of IL-2. Those with hepatitis C virus (HCV) associated cirrhosis had the highest value for IL-6, IL-8, IL-10, MCP-1 and VEGF. Those with cardiac disease had the highest level of TNF-α and EGF. The calculated serum-ascites gradient for the cardiac and malignant disease groups had a greater frequency of negative values signifying greater levels of IL-8, IL-10 and MCP-1 in ascites than did those with alcohol or HCV disease. CONCLUSION: These data document important differences in the cytokine and growth factor levels in plasma, ascitic fluid and the calculated plasma-ascites fluid gradients in cirrhotics requiring a large volume paracentesis. These differences may be important in determining the risk for bacterial peritonitis.

HIV/HCV COINFECTION


Abstract: Human immunodeficiency virus (HIV) coinfection with hepatitis C virus (HCV) is associated with an increased HCV RNA level, as well as a more rapid progression to cirrhosis and end-stage liver disease. However, the mechanism underlying this effect is largely unknown. Here, we investigated the role of HIV-1 Vpr in HCV infection and clearly demonstrated that Vpr increased the replication of both the infectious HCV full-length genome and the subgenomic replicon. We also demonstrated that Vpr increased HCV infection by enhancing RNA replication but not viral entry or translation. Further, we showed that Vpr could partially overcome the anti-HCV effect of PEG-IFN. Our findings not only partially explain the clinical observation that patients coinfected with HIV and HCV have higher levels of HCV RNA and viral load than HCV mono-infected patients but also provide important information for HCV treatment in HIV/HCV coinfected patients.


Background. Individuals infected with human immunodeficiency virus (HIV) appear to age faster than the general population, possibly related to HIV infection, antiretroviral therapy, and/or social/environmental factors. We evaluated leukocyte telomere length (LTL), a marker of cellular aging, in HIV-infected and uninfected adults. Methods. Clinical data and blood were
collected from Children and women: AntiRetrovirals and the Mechanism of Aging (CARMA) cohort study participants. Variables found to be important in univariate analysis were multivariate model candidates. **Results.** Of the 229 HIV-infected and 166 HIV-uninfected participants, 76% were women, and 71% were current/previous smokers. In a multivariate model of all participants, older age (P < .001), HIV infection (P = .04), active hepatitis C virus (HCV) infection (P = .02), and smoking (P < .003) were associated with shorter LTL. An interaction was detected, whereby smoking was associated with shorter LTL in HIV-uninfected subjects only. Among those, age and smoking (P ≤ .01) were related to shorter LTL. In 2 models of HIV-infected individuals, age (P ≤ .002) and either active HCV infection (P = .05) or peak HIV RNA ≥100 000 copies/mL (P = .04) were associated with shorter LTL, whereas other HIV disease or treatment parameters were unrelated. **Conclusions.** Our results suggest that acquisition of HIV and viral load are primarily responsible for the association between HIV-positive status and shorter LTL. The lack of association between LTL and time since HIV diagnosis, antiretroviral treatment, or degree of immune suppression would implicate HIV infection-related factors rather than disease progression or treatment. Smoking effects on LTL appear masked by HIV, and HCV infection may accelerate LTL shortening, particularly in coinfected individuals. The effect of early therapeutic intervention on LTL in HIV and HCV infections should be evaluated.


**OBJECTIVES:** The incidence of sexually transmitted hepatitis C virus (HCV) reinfection is on the rise in HIV-infected men who have sex with men (MSM). Data on natural history of acute hepatitis C and possible factors associated with spontaneous clearance are limited. The aim of this study was to analyse the outcome of HCV reinfections in HIV-positive MSM. **METHODS:** A retrospective analysis was carried out on patients with more than one sexually acquired HCV infection who were diagnosed at four major German HIV and hepatitis care centres. Reinfection was defined by genotype or phylogenetic clade switch, detectable HCV RNA after a sustained virological response (SVR) or after spontaneous clearance (SC). **RESULTS:** In total, 48 HIV-positive MSM were identified with HCV reinfection, among them 11 with a third episode and one patient with four episodes. At the first episode, 43 and five patients had an SVR and SC, respectively. The second episode was accompanied by a genotype switch in 29 patients (60%). Whereas 30 and nine patients showed an SVR and SC, respectively, eight patients developed chronic hepatitis. Neither HCV genotype switch nor interleukin-28B genotype was associated with SC. However, SC rates at the second episode were higher for patients with SC at the first episode compared with patients without SC (60 vs. 14%, respectively; P = 0.03). Two patients with SC at the first episode were reinfected with the same genotype. **CONCLUSIONS:** Multiple reinfections in HIV-infected MSM do occur, with or without genotype switch, and with prior SC of previous episodes. In this large case series, except for SC at the first episode, no factor was of value in clinical decision-making for early therapeutic intervention in acute HCV reinfection.

Around 10-15% of the 35 million people living with HIV worldwide have chronic hepatitis C virus (HCV) infection and are prone to develop liver-related complications. Exposure to HCV is almost universal among injecting drug users and is on the rise among homosexual men. Response to peginterferon-ribavirin therapy is generally lower in coinfection compared to HCV monoinfection. For this reason, the advent of direct-acting antivirals (DAA) is eagerly awaited for this population. The results of trials using DAA in coinfection show that treatment response rates are similar to those obtained in HCV monoinfection. Thus, HIV should no longer be considered as a "special" population, as long as antiretroviral therapy is given and drug interactions are taken into account. Envisioning HCV eradication from the HIV population faces major challenges ahead, including identification of the large number of undiagnosed individuals, and ensuring wide access to the best but often expensive HCV medications. This article forms part of a symposium in Antiviral Research on "Hepatitis C: next steps toward global eradication".


The impact of hepatitis C virus (HCV)-related characteristics such as genotype, viral load or liver fibrosis on the chances of achieving sustained HIV suppression in coinfected patients is not fully documented. We examined the relationship between both HIV/HCV-related and sociobehavioural characteristics and HIV sustained viral suppression (SVS) in 897 patients included in the ANRS CO13 HEPAVIH cohort. The main outcome variable was HIV SVS, defined as at least two consecutive undetectable HIV viral loads. Among the 897 HIV/HCV-coinfected patients, 419 (47%) had received HCV therapy at least once, and 103 patients (25%) had experienced an HCV sustained virologic response (SVR). In multivariate analysis, older age [odds ratio (OR) 1.23 for each period of 5 years of age, 95% confidence interval (CI) 1.02-1.49; P=0.03], a higher level of school education (OR 1.92, 95% CI 1.04-3.56; P=0.04), good adherence to HIV therapy (OR 2.05, 95% CI 1.23-3.43; P=0.006) and HCV SVR (OR 1.81, 95% CI 1.01-3.26; P=0.04) remained significantly associated with HIV SVS. In contrast, triple nucleoside reverse transcriptase inhibitor (NRTI) regimens were associated with failure to achieve HIV SVS (OR 0.50, 95% CI 0.27-0.94; P=0.03). Our results show that HCV SVR is associated with a higher likelihood of achieving HIV SVS. With the advent of direct-acting anti-HCV drugs, a marked increase in the rate of virologic response is observed in coinfected patients. So, further research is needed to determine whether suppression of HCV replication could be associated with a higher efficacy of antiretroviral therapy.

this study was to quantify and compare the HCV-specific memory B-cell response between chronic and resolved HCV-infected individuals. A secondary goal was to examine if HIV-specific memory B-cell responses are maintained during HCV co-infection. **STUDY DESIGN:** HCV core protein- and HIV-specific memory B-cell responses were examined in HIV/HCV-infected individuals treated 4-30 weeks after HCV diagnosis. Memory B-cell frequencies were compared between chronically and transiently infected individuals. **RESULTS:** Chronically infected individuals had vigorous HCV-specific memory B-cell responses and antibodies, whereas subjects with transient viremia showed low or undetectable virus-specific B-cell responses. In addition, chronically HIV/HCV-infected subjects had robust HIV-specific memory B-cell responses. **CONCLUSIONS:** Whereas chronic HCV infection induces virus-specific antibodies and memory B-cells, transient infection in individuals with sustained viral response to therapy does not stimulate a durable HCV-specific B-cell response indicating that the formation of long-lived virus-specific B-cells is suppressed in the early phase of infection. This may contribute to the inability to spontaneously clear HCV infection.


**PURPOSE OF REVIEW:** We reviewed the pharmacokinetic interactions between direct-acting antivirals against hepatitis C virus (HCV) and antiretroviral agents. **RECENT FINDINGS:** Most relevant pharmacokinetic studies involve healthy individuals and refer to the already licensed HCV protease inhibitors, boceprevir and telaprevir. Data from a phase II clinical trial question the clinical relevance of the interactions between boceprevir and HIV protease inhibitors. The use of a higher dose of telaprevir appears to offset the effect of efavirenz on telaprevir metabolism according to another phase II trial. Boceprevir and particularly telaprevir substantially increase the exposure to maraviroc, similarly to other potent CYP3A4 inhibitors. Different dosages of faldaprevir and daclatasvir have been recommended to be used in combination with a boosted HIV protease inhibitor vs. an efavirenz-based antiretroviral regimen. HIV protease inhibitors appear to substantially increase the exposure to simeprevir. The interactions between sofosbuvir and most antiretroviral agents do not appear to be of clinical relevance or to require dosage modifications. **SUMMARY:** The drug-drug interaction studies for HCV direct-acting antivirals and antiretrovirals are important in determining the appropriate drug combinations and dosages. The clinical implications of these interactions need further assessment in different categories of patients, including those with cirrhosis.

**Epidemiology, Diagnostics, and Miscellaneous Works**


**Background.** Numbers of deaths in hepatitis C virus (HCV)-infected persons recorded on US death certificates have been increasing, but actual rates and causes of death in them have not been well elucidated. **Methods.** Disease-specific, liver- and non-liver-related, mortality for HCV-infected patients in an observational cohort study, the Chronic Hepatitis Cohort Study (CHeCS) at four US health care systems, were compared with Multiple Cause of Death (MCOD)
data in 12 million death certificates in 2006-2010. Pre-mortem diagnoses, liver biopsies, and FIB-4 scores (a non-invasive measure of liver damage) were examined. **Results.** Of 2,143,369 adult patients seen at CHeCS sites in 2006-2010, 11,703 (0.5%) had diagnosed chronic HCV infection, and 1,590 (14%) died. CHeCS decedents were born from 1945-1965 (75%), white (50%), and male (68%); mean age of death was 59 years, 15 years younger than MCOD deaths. The age-adjusted mortality rate for liver disease in CHeCS was twelve times higher than the MCOD rate. Before death, 63% had medical record evidence of chronic liver disease, 76% had elevated FIB-4 scores, and of those biopsied 70% had moderate or worse liver fibrosis. However, only 19% of all CHeCS decedents and only 30% of those with recorded liver disease had HCV listed on their death certificates. **Conclusions.** HCV infection is greatly under-documented on death certificates. The 16,622 persons with HCV listed in 2010 may represent only one-fifth of about 80,000 HCV-infected persons dying that year, at least two-thirds of whom (53,000 patients) would have pre-mortem indications of chronic liver disease.


**Background.** Infection with hepatitis C virus (HCV) increases the risk of death from liver and non-liver related diseases. Co-infection with HIV further increases this risk. **Methods.** Surveillance data (2000-2010) and mortality data (2000 - 2011) maintained by the New York City Department of Health and Mental Hygiene (DOHMH) were deterministically cross-matched. Factors associated with and causes of death among HCV-infected adult decedents were analyzed. **Results.** Between 2000 and 2011, 13,307 HCV mono-infected adults died, and 5,475 adults co-infected with HCV/HIV died. Decedents with HCV mono-infection were more likely to have died of liver cancer (OR=9.2), drug-related causes (OR=4.3), and cirrhosis (OR=3.7) as compared with persons with neither infection. HCV/HIV co-infected decedents were more likely to have died of liver cancer (OR=2.2) and drug-related causes (OR=3.1) as compared with persons with neither infection. Among co-infected decedents, 53.6% of deaths were attributed to HIV/AIDS; and 94% of deaths occurred prematurely, before age 65. Among persons with HCV who died, over half died within three years of a hepatitis C report to DOHMH. **Conclusion.** HCV-infected adults were at increased risk of dying and of dying prematurely.


An association of hepatitis C virus (HCV) infection with diabetes has been reported in many studies, but few have been population-based and applied standard criteria for diabetes diagnosis. We examined this relationship using recent population-based data from the U.S. National Health and Nutrition Examination Survey. 15,128 adult participants in the 1999-2010 surveys had data on diabetes status and serum HCV antibody (anti-HCV) or HCV RNA. Using American Diabetes Association criteria, diabetes was defined as a health care provider diagnosis, serum hemoglobin A1C (A1C) ≥6.5%, or fasting plasma glucose (FPG) ≥126 mg/dL; pre-diabetes as A1C 5.7%-<6.5% or FPG 100-<126 mg/dL; and normal glucose as A1C <5.7% and FPG <100 mg/dL. Odds ratios (OR) for diabetes and pre-diabetes, comparing persons with HCV infection to those without, were adjusted for demographics, BMI, C-reactive protein, smoking, drinking,
and blood transfusion before 1992. Among participants without diabetes, we compared mean insulin resistance, estimated using homeostasis model assessment (HOMA-IR), by HCV status. The overall prevalence of anti-HCV+ was 1.7%, of HCV RNA+, 1.1%, of diabetes, 10.5%, and of pre-diabetes, 32.8%. The prevalence of diabetes and pre-diabetes did not differ by HCV status. In multivariate-adjusted analysis, diabetes remained unassociated with anti-HCV (OR=1.0, 95% confidence interval (CI), 0.6-1.7) or with HCV RNA (OR=1.1, 95% CI, 0.6-1.9). In contrast, elevated alanine aminotransferase and gamma glutamyltransferase activities were associated with diabetes regardless of HCV status. HOMA-IR was not associated with HCV markers in unadjusted or multivariate-adjusted analyses (p>0.05).

**Conclusion.** In the U.S. population, HCV was not associated with diabetes, or with insulin resistance among persons with normal glucose. Previously reported relationships of HCV with diabetes were possibly attributable to the effect of elevated liver enzymes. (Hepatology 2014:).


Anti-HCV testing is the first step to diagnose hepatitis C. Although anti-HCV assay performance improved during the last 2 decades, very high sensitivity required for screening may lead to limitations in specificity. Thus, there remains an uncertainty how to interpret anti-HCV test results with a borderline signal-to-cut-off ratio. Comparison was made of concordance and performance of four licensed anti-HCV assays in samples with borderline signal-to-cut-off ratios. Out of 12,090 consecutive samples tested for anti-HCV with the Abbott Architect Anti-HCV assay over a period of 29 months, 95 plasma samples with a signal-to-cut-off ratio between 0.5 and 2 were selected for this study. All samples were re-tested with the Enzygnost Anti-HCV version 4.0, the Ortho anti-HCV version 3.0, and the Monolisa anti-HCV-Plus version 2 assays. Discordant samples were classified by additional immunoblot testing. Overall, only 52% of the Architect borderline samples gave similar results in all four assays. Inter-assay concordance ranged between 58% and 80%. The highest discordance was observed between the Architect and the Monolisa assay (42%). In contrast, a high level of concordance was found between the Enzygnost and Ortho assays (80%). The Monolisa was best to identify negative samples (100%), while the Enzygnost correctly classified most of the positive samples (96%). Anti-HCV antibody assays show significant variation in classifying samples with low signal-to-cut-off ratios. Different performances may have cost and management implications, as false-positive results are not infrequent. However, sensitivities were good for all assays if indeterminate results are not considered as negative.


**BACKGROUND:** To estimate the incidence of Hepatitis C virus (HCV) and the predictive factors through repeated routine laboratory analyses. **METHODS:** An observational cohort study was carried out in Quatre Camins Prison, Barcelona. The study included subjects with an initial negative HCV result and routine laboratory analyses containing HCV serology from 1992 to 2011. The incidence of infection was calculated for the study population and for sub-groups
by 100 person-years of follow-up (100 py). The predictive factors were determined through Kaplan-Meier curves and a Cox regression. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. RESULTS: A total of 2,377 prisoners were included with a median follow-up time of 1,540.9 days per patient. Among the total population, 117 HCV seroconversions were detected (incidence of 1.17/100 py). The incidence was higher between 1992 and 1995 (2.57/100 py), among cases with HIV co-infection (8.34/100 py) and among intravenous drug users (IDU) without methadone treatment (MT) during follow-up (6.66/100 py). The incidence rate of HCV seroconversion among cases with a history of IDU and current MT was 1.35/100 py, which is close to that of the total study population. The following variables had a positive predictive value for HCV infection: IDU (p<0.001; HR=7.30; CI: 4.83-11.04), Spanish ethnicity (p=0.009; HR=2.03; CI: 1.93-3.44) and HIV infection (p=0.015; HR=1.97; CI: 1.14-3.39).

CONCLUSION: The incidence of HCV infection among prisoners was higher during the first part of the study and among IDU during the entire study period. Preventative programs should be directed toward this sub-group of the prison population.


BACKGROUND: The hepatitis C virus (HCV) antibody test alone does not distinguish current from resolved infections. AIM: The study aimed to describe the percentage of current HCV infection, defined by HCV RNA positivity, among those tested positive for anti-HCV, and to examine characteristics of those with current infection. METHODS: Using nationally representative data from the 2003 to 2010 National Health and Nutrition Examination Surveys, descriptive analyses and regressions were performed on data from anti-HCV-positive adults aged ≥40 years. RESULTS: Of 13,909 participants examined, 304 were anti-HCV-positive. Of these, 238 or 75.3 % [95 % confidence interval (CI) 67.5-81.8 %] had detectable viral RNA. The percentage of current, unresolved HCV infection was highest among non-Hispanic Blacks (91.1 %) and lowest among those with a college education (57.3 %). In multivariate analyses, non-Hispanic Blacks were more likely to have current HCV infection compared to non-Hispanic Whites (adjusted odds ratio 3.9, 95 % CI 1.6-9.2). Among persons with current HCV infection, most had elevated alanine aminotransferase (56.5 %) or aspartate aminotransferase (71.8 %) levels, but only 35.3 % reported having been diagnosed with any abnormal liver conditions. Excessive alcohol drinking was reported by 27.3 % of participants with current HCV infection. CONCLUSIONS: Among adults aged ≥40 years who had ever been infected with HCV, approximately three-quarters had current, unresolved HCV infection. Non-Hispanic Blacks were more likely to have current infection than non-Hispanic Whites. The majority of those with current infection had abnormal liver function tests but had not received appropriate diagnoses. Many currently infected persons would benefit from lifestyle modifications to avoid the multiplicative effect of alcohol on HCV infection.


Hepatitis C virus (HCV) is a major cause of liver disease and hepatocellular carcinoma
The treatment of chronic hepatitis C has fundamentally changed since the approval of the first direct-acting antivirals (DAA) in 2011. In addition to telaprevir and boceprevir, in 2014 two new NS3 protease inhibitors (simeprevir and faldaprevir), one non-nucleoside polymerase inhibitor (sofosbuvir) and one NS5a replication complex inhibitor (daclatasvir) have expanded the treatment options for chronic hepatitis C. Resistance-associated variants (RAV) are naturally produced during the HCV life cycle. The frequency of RAVs within HCV quasispecies mainly depends on their replicational fitness. Variants conferring resistance to nucleos(t)ide analogues have not been detected, and the majority of NS3 protease-resistant variants are present at low frequencies (0.1-3%) before initiation of DAA-based therapies. However, the Q80K variant conferring resistance to simeprevir has been observed in 9-48% of untreated HCV genotype 1a-infected patients, leading to reduced SVR rates. Resistant variants are detectable in the majority of patients with treatment failure to NS3 protease inhibitor- or NS5a inhibitor-based antiviral therapy. Long-term follow-up studies by population-based sequence analysis have shown the disappearance of resistant variants in the majority of patients, with median times to loss of mutations of 4-64 weeks. For the nucleotide analogue sofosbuvir, the emergence of the S282T resistant variant has been observed only in single patients, with reversion to wild-type within several weeks. Data are sparse on retreatment of patients with the same DAA or the same class of DAAs. However, retreatment with a different class of DAAs after failure of NS3 protease inhibitor-based therapy has been successful in small studies. This article forms part of a symposium in Antiviral Research on "Hepatitis C: next steps toward global eradication."

BACKGROUND: Currently, sharing of drug paraphernalia is the main form of HCV transmission worldwide. In South America, consistent findings indicate that shared sniffing equipment is an important factor in the spread of HCV among non-injecting drug users. Epidemiological data on the status of HCV infection in illicit drug users in the Amazon region are scarce, although reports of clinical cases of hepatitis or pathologies associated with HCV
infection in other population groups are numerous. Thereby, this study investigated the prevalence, genotype frequency, and epidemiological factors associated with HCV infection in non-injecting drug users in the state of Pará, eastern Amazon. **RESULTS:** During 2008-2011, 300 non-injecting drug users attending drug-treatment centers participated in this study. Most non-injecting drug users were male (63.7%). The mean age was 32.5 years. The non-injecting drugs most consumed were: cannabis (15.6%), cocaine paste (21.3%), and oxi cocaine (25.7%). Tobacco (60.9%) and alcohol (79.4%) were also commonly consumed. One hundred six (35.1%; CI 95%: 29.8 - 41.1) non-injecting drug users presented anti-HCV antibodies by EIA. The HCV-RNA prevalence was 28.0% (95% CI: 20.6 - 35.8). Genotypes 1 (76.9%) and 3 (23.1%) of HCV have been identified. A multivariate analysis demonstrated that HCV infection was independently associated with the following factors: "age (≥ 35 years)" , "tattoos", "use of a needle or syringe sterilized at home", "shared use of drug paraphernalia", "uses drugs for more than 5 years", and "use of drugs everyday". **CONCLUSIONS:** This study revealed a high prevalence of HCV infection in non-injecting drug users, and most infections are occasioned by genotype 1. Likely, HCV transmission is associated with the tattoos, the use of needle or syringe sterilized at home by people over the age of 35 years, and sharing, time and frequency of use of non-injecting drugs. These findings should serve as an incentive for the establishment of a program of Hepatitis C prevention and control by the local public-health authorities in order to develop effective policies and strategies for contain the spread of HCV infection.


Work productivity is impacted in hepatitis C virus (HCV)-infected patients and has been linked to treatment. In two Phase 3 trials, ADVANCE and ILLUMINATE, treatment-naïve genotype 1 chronic HCV-infected patients received 12-week telaprevir (T) with 24 (T12PR24)- or 48 (T12PR48)-week peginterferon alfa-2a/ribavirin. The objective of this analysis was to examine the impact of chronic HCV infection and its treatment with combination therapy on work productivity. The 5-item, self-reported work productivity questionnaire (WPQ) was administered in Phase 3 trials to assess unemployment status, days unable to work due to HCV/treatment, reduced hours worked and impact on productivity in prior 4 weeks. Descriptive statistics and multivariate regression analyses were employed in analyses of pooled trial data. About 1147 patients were included; 22% (n = 255) were unemployed at baseline, with 8% being unemployed due to health reasons. At week 12, there were no differences by treatment regimen in the number of days unable to work. At week 48, improvements were observed earlier among patients receiving the shorter duration of T combination treatment. Mean (95% CI) change from baseline in days unable to work was -0.48 (-0.85, -0.11) days for T12PR24, 1.43 (0.63, 2.24) days for T12PR48 and 1.24 (0.18, 2.30) days for PR48 with placebo. Predictors of days unable to work were identified and include demographic characteristics, pretreatment and on-treatment levels of fatigue, as well regional variation. In post hoc analyses of the ADVANCE and ILLUMINATE trials, work productivity decreased during the initial 12 weeks regardless of treatment group.

Introduction: No data are available about the prediction of long-term survival using repeated non-invasive tests of liver fibrosis in chronic hepatitis C (CHC). We aimed to assess the prognostic value of 3-year liver stiffness measurement (LSM), APRI, and FIB-4 evolution in CHC. Patients and methods: CHC patients with two LSM (1000-1500 days interval) were prospectively included. Blood fibrosis tests APRI and FIB-4 were calculated the day of baseline (bLSM) and follow-up (fLSM) LSM. Evolution of fibrosis tests was expressed as delta: (follow-up-baseline results)/duration. Date and cause of death were recorded during follow-up that started the day of fLSM. Results: 1025 patients were included. Median follow-up after fLSM was 38.0 months (IQR: 27.7-46.1) during which 35 patients died (14 liver-related death) and 7 had liver transplantation. Prognostic accuracy (Harrell C-index) of multivariate models including baseline and delta results was not significantly different between LSM and FIB-4 (p≥0.24) whereas FIB-4 provided more accurate prognostic models than APRI (p=0.03). By multivariate analysis including LSM variables, overall survival was independently predicted by bLSM, delta (dLSM), and SVR. Prognosis was excellent in patients having bLSM <7 kPa, SVR, or no increase (<1 kPa/year) in 7-14 kPa bLSM. Prognosis was significantly impaired in patients with increase (≥1 kPa/year) in 7-14 kPa bLSM, or decrease (≤0 kPa/year) in ≥14 kPa bLSM (p=0.949 between these two groups). Patients with increase (>0 kPa/year) in ≥14 kPa bLSM had the worst prognosis. Baseline and delta FIB-4 also identified patient subgroups with significant different prognosis. Conclusion: Three-year evolution of non-invasive tests of liver fibrosis has a strong prognostic value in CHC patients. These tests should be repeated to monitor patients and predict their outcome. (Hepatology 2014:).


BACKGROUND: In an attempt to curtail the rising morbidity and mortality from undiagnosed HCV (hepatitis C virus) in the United States, screening guidelines have been expanded to high-risk individuals and persons born 1945-1965. Community-based screening may be one strategy in which to reach such persons; however, the acceptance of HCV testing, when many high-risk individuals may not have access to HCV specific medications, remains unknown. METHODS: We set out to assess attitudes about HCV screening and knowledge about HCV disease at several community-based testing sites that serve high-risk populations. This assessment was paired with a brief HCV educational intervention, followed by post-education evaluation. RESULTS: Participants (n = 140) were surveyed at five sites; two homeless shelters, two drug rehabilitation centers, and a women's "drop-in" center. Personal acceptance of HCV testing was almost unanimous, and 90% of participants reported that they would still want to be tested even if they were unable to receive HCV treatment. Baseline hepatitis C knowledge was poor; however, the brief educational intervention significantly improved knowledge and increased acceptability of testing when medical access issues were explicitly stated. CONCLUSIONS: Despite inconsistencies in access to care and treatment, high-risk communities want to know their HCV status. Though baseline HCV knowledge was poor in this population, a brief on-site educational intervention improved both knowledge and acceptability of HCV testing and care. These data support the establishment of programs that utilize community-based screening, and also provide
initial evidence for acceptance of the implementation of the recently expanded screening guidelines among marginalized communities.


**AIM:** To investigate the factors other than fibrosis stage correlating with acoustic radiation force impulse (ARFI) elastography in chronic hepatitis C. **METHODS:** ARFI elastography was performed in 108 consecutive patients with chronic hepatitis C who underwent a liver biopsy. The proportion of fibrosis area in the biopsy specimens was measured by computer-assisted morphometric image analysis. **RESULTS:** ARFI correlated significantly with fibrosis stage (β = 0.1865, P < 0.0001) and hyaluronic acid levels (β = 0.0008, P = 0.0039) in all patients by multiple regression analysis. Fibrosis area correlated significantly with ARFI by Spearman's rank correlation test but not by multiple regression analysis. ARFI correlated significantly with body mass index (BMI) (β = -0.0334, P = 0.0001) in F 0 or F 1, with γ-glutamyltranspeptidase levels (β = 0.0048, P = 0.0012) in F 2, and with fibrosis stage (β = 0.2921, P = 0.0044) and hyaluronic acid levels (β = 0.0012, P = 0.0025) in F 3 or F 4. The ARFI cutoff value was 1.28 m/s for F ≥ 2, 1.44 m/s for F ≥ 3, and 1.73 m/s for F 4. **CONCLUSION:** ARFI correlated with fibrosis stage and hyaluronic acid but not with inflammation. ARFI was affected by BMI, γ-glutamyltranspeptidase, and hyaluronic acid in each fibrosis stage.


**BACKGROUND & AIMS:** Given an appreciable risk of adverse-effects, current therapies for chronic hepatitis C virus (HCV) infection pose a dilemma to patients. We explored, via simulation modelling, patient-important benefits of attaining a Sustained Viral Response (SVR). **METHODS:** We created the HCV Individualised Treatment-decision model (the HIT-model) to simulate, on a per patient basis, the lifetime course of HCV-related liver disease according to two distinct scenarios: (i) SVR attained, and (ii) SVR not attained. Then, for each model subject, the course of liver disease under these alternative scenarios was compared. The benefit of SVR was considered in terms of two patient-important outcomes: (1) The percent-probability that SVR confers additional life-years; and (2) The percent-probability that SVR confers additional healthy life-years, where "healthy" refers to years spent in compensated disease states (i.e. the avoidance of liver failure). **RESULTS:** The benefit of SVR varied strikingly. It was lowest for patients aged 60 years with initially mild fibrosis; 1.6% (95% CI: 0.8-2.7) and 2.9% (95% CI: 1.5-4.7) probability of gaining life-years and healthy life-years, respectively. Whereas it was highest for patients with initially compensated cirrhosis aged 30 years; 57.9% (95%CI: 46.0-69.0) and 67.1% (95%C: 54.1-78.2) probability of gaining life-years and healthy life-years, respectively. **CONCLUSIONS:** For older patients with less advanced liver fibrosis, SVR is less likely to confer benefit when measured in terms of averting liver failure and premature death. These data have important implications. Foremost, it may inform the contemporary patient dilemma of immediate treatment with existing therapies (that have poor adverse effect profiles) versus awaiting future regimens that promise better tolerability.

There is growing acknowledgment that social, structural, and environmental forces produce vulnerability to health harms among people who inject drugs (PWID), and safer environment interventions (SEI) have been identified as critical to mitigating the impacts of these contextual forces on drug-related harm. To date, however, SEIs have been under-theorized in the literature, and how they minimize drug-related risks across intervention types and settings has not been adequately examined. This article presents findings from a systematic review and meta-synthesis of qualitative studies reporting PWID's experiences with three types of SEIs (syringe exchange programmes, supervised injection facilities and peer-based harm reduction interventions) published between 1997 and 2012. This meta-synthesis sought to develop a comprehensive understanding of SEIs informed by the experiences of PWID. Twenty-nine papers representing twenty-one unique studies that included an aggregate of more than 800 PWID were included in this meta-synthesis. This meta-synthesis found that SEIs fostered social and physical environments that mitigated drug-related harms and increased access to social and material resources. Specifically, SEIs: (1) provided refuge from street-based drug scenes; (2) enabled safer injecting by reshaping the social and environmental contexts of injection drug use; (3) mediated access to resources and health care services; and, (4) were constrained by drug prohibition and law enforcement activities. These findings indicate that it is critical to situate SEIs in relation to the lived experiences of PWID, and in particular provide broader environmental support to PWID. Given that existing drug laws limit the effectiveness of interventions, drug policy reforms are needed to enable public health, and specifically SEIs, to occupy a more prominent role in the response to injection drug use.


With the approval of second-wave direct-acting antivirals simeprevir, sofosbuvir and faldaprevir in 2014-2015, for genotype 1 hepatitis C, patients and doctors will have more treatment options. During a first period, these treatments will still be used with peginterferon and ribavirin. The second wave of IFN-based triple therapy will have benefits and risk. These treatments have the following advantages: higher efficacy with more patient candidates for a shorten treatment duration (12-24 weeks, instead of 48 weeks). These new treatments appear to have a better safety profile than first generation, with no additional increase in anaemia over peginterferon/ribavirin. Then, these treatments are to take for patients with a decrease in pill burden (these three direct-acting antivirals are given orally one pill a day). Simeprevir and sofosbuvir may be approved in the US and Europe, in 2014, at the time this manuscript will be released. Approval of faldaprevir will follow. These direct-acting antivirals with many others will hopefully be combined in future interferon-free regimens. The goal of this review to summarize the results and safety of simeprevir, faldaprevir and sofosbuvir, to advise physicians and to inform patients on the benefits and risks of these second-wave IFN-based regimens for HCV genotype infection.

Genome-wide association studies recently revealed that certain interleukin-28B (IL28B) polymorphisms are strongly associated with responses to pegylated interferon (PEG-IFN) and ribavirin (RBV) therapy in patients chronically infected with hepatitis C virus (HCV) genotype 1, as well as with spontaneous clearance of HCV. Subsequent reports revealed that IL28B genotypes also affect treatment efficacy in chronic infection with other HCV genotypes. Furthermore, there have been several reports that implicate IL28B genotypes in inflammatory status, progression of fibrosis and adverse clinical outcomes in chronic hepatitis C (CHC). Therapy of CHC recently entered a new era with the deployment of direct-acting antivirals. These include nonstructural 3/4A protease inhibitors which have shown promise in combination with PEG-IFN/RBV in several clinical trials. IFN-free therapy is expected to be useful especially in IFN-resistant patients and may become the standard of care in the future. Several clinical trials have revealed an association between IL28B genotype and treatment efficacy in triple therapy or IFN-free regimens. On the other hand the mechanism of the effect of IL28B on HCV infection has not yet been elucidated. Recently, it was shown that the polymorphism of IFN-lambda 4 (IFNL4) is in high linkage disequilibrium with that of near IL28B, and more strongly associated with spontaneous or treatment-induced HCV clearance than IL28B genotypes, especially in individuals of African ancestry. This finding provides new insights into the genetic regulation of HCV clearance and its clinical management. IL28B genotyping will be also useful for personalized CHC treatment in the forthcoming era of direct-acting antivirals.

LIVER CANCER


BACKGROUND & AIMS: Ultrasound surveillance does not detect early-stage hepatocellular carcinomas (HCCs) in some patients with cirrhosis, although the reasons for this have not been well studied. We assessed the rate at which ultrasound fails to detect early-stage HCCs and factors that affect its performance. METHODS: We collected information on 1170 consecutive patients included in the Italian Liver Cancer (ITA.LI.CA ) database who had Child-Pugh A or B cirrhosis and were diagnosed with HCC during semi-annual or annual ultrasound surveillance, from January 1987 through December 2008. Etiologies included: hepatitis C virus infection (59.3%), alcohol abuse (11.3%), hepatitis B virus infection (9%), a combination of factors (15.6%), and other factors (4.7%). Surveillance was considered to be a failure when patients were diagnosed with HCC at a stage beyond the Milan criteria (1 nodule ≤5 cm or ≤3 nodules each ≤3 cm). RESULTS: Ultrasound surveillance failed to detect HCC in 34.3 % of patients and more often in the annual program than in the semiannual one. (41.3% vs 32.2 % ; P<0.01). Nearly half of surveillance failures were associated with at least one indicator of aggressive HCC (levels of AFP >1000 ng/ml, infiltrating tumors, or vascular invasion and metastases). Semi-annual surveillance, female sex, Child-Pugh class A, and AFP levels ≤ 200 ng/ml were independently associated with successful ultrasound screening for HCC. CONCLUSION: Based
on analysis of surveillance for HCC in patients with cirrhosis, the efficacy of ultrasound-based screening is acceptable. Ultrasound is least effective in identifying aggressive HCC, and at surveillance intervals >6 months.


**AIMS:** Aim of the study was to assess if host (immunogenetic traits, age, sex), exogenous (alcohol) or viral factors (viral type, past HBV infection) might affect the progression of chronic hepatitis C to liver decompensation or the development of HCC in a cohort of patients exposed to a single blood transfusion prior to the introduction of anti-HCV screening. **METHODS:** Two hundred and forty-eight patients with a history of a single exposure to blood or blood products prior to 1990 were retrospectively considered. Patients were devoid of other risk factors of liver disease or immunosuppression and naïve to antiviral therapies. Eight baseline variables were assessed: age at transfusion, sex, HBV core antibody, immunogenetic profile (DRB1*11, DRB1*1104, DRB1*07), HCV genotype and alcohol consumption. **RESULTS:** The follow-up was 22 (SD 11) years. Sixty-eight patients (27%) progressed to hepatic decompensation over a median period of 22.5 years (IQR: 14-30) and 41 patients (16%) developed HCC over a median period of 31 years (IQR: 24 - 38). The cumulative incidence of liver failure was 0.4% (95%CI: 0.1 - 3.1), 4.9% (95%CI: 2.6 - 9.3) and 16.2% (95%CI: 10.4 - 24.7) at 10, 20 and 30 years after blood transfusion, respectively. By univariate analysis, only age at transfusion was correlated with the risk of decompensation. Stratifying the age of transfusion by tertiles, the incidence of hepatic decompensation was 0.7% per year in patients transfused at ≤24 years of age as compared with 1.2% and 1.9% per year in those transfused at 25-35 and >36 years of age, respectively (HR 5.5, 95%CI: 2.78-10.7, p<0.001). The risk of HCC development was correlated by univariate analysis with age at transfusion (as continuous variable, HR 1.12, 95% CI 1.08-1.16 per year of age, p<0.001, >36 compared to ≤24 years, HR 10.3, 95% CI 3.9-26.9, p<0.001) and male sex (HR 4.2, 95% CI 1.7-10, p=0.001). Multivariate analysis confirmed age at transfusion and male sex as independent predictors of HCC development (HR 1.12 per year [95% CI: 1.08-1.16], p<0.001 and HR 5.4 [95% CI 2.2-13.2], p<0.001, respectively)

**CONCLUSIONS:** In patients with transfusion-acquired HCV infection, age at transfusion affect the risk for hepatic decompensation. Age at transfusion and male sex are also independent risk factors for HCC development.

**Liver let die: oxidative DNA damage and hepatotropic viruses.** Higgs MR, Chouteau P, Lerat H. J Gen Virol. 2014 Feb 4. doi: 10.1099/vir.0.059485-0. [Epub ahead of print]


Chronic infections by the hepatotropic viruses hepatitis B virus (HBV) and hepatitis C virus (HCV) are major risk factors for the development of hepatocellular carcinoma (HCC). It is estimated that more than 700,000 individuals per year die from hepatocellular carcinoma, and around 80% of HCC is attributable to HBV or HCV infection. Despite the clear clinical importance of virus-associated HCC, the underlying molecular mechanisms remain largely elusive. Oxidative stress, in particular DNA lesions associated with oxidative damage, play a major contributory role in carcinogenesis, and are strongly linked to the development of many cancers, including HCC. A large body of evidence demonstrates that both HBV and HCV induce
hepatic oxidative stress, with increased oxidative DNA damage being observed both in infected individuals and in murine models of infection. Here, we review the impact of HBV and HCV on the incidence and repair of oxidative DNA damage. We begin by giving a brief overview of oxidative stress and the repair of DNA lesions induced by oxidative stress. We then review in detail the evidence surrounding the mechanisms by which both viruses stimulate oxidative stress, before focusing on how the viral proteins themselves may perturb the cellular response to oxidative DNA damage, impacting upon genome stability and thus hepatocarcinogenesis.