Consensus interferon plus ribavirin for hepatitis C genotype 3 patients previously treated with pegylated interferon plus ribavirin.
Abbas Z1, Tayyab GN2, Qureshi M1, Memon MS3, Subhan A1, Shakir T1, Jafri W1, Hamid S1.
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BACKGROUND: Not enough data are available about the effectiveness of consensus interferon (CIFN) among HCV genotype 3 patients who failed to respond to pegylated interferon and ribavirin. OBJECTIVES: We aimed to assess the efficacy and safety of CIFN and ribavirin in non-responders and relapers to pegylated interferon with ribavirin therapy. PATIENTS AND METHODS: This open-label investigator-initiated study included 44 patients who received CIFN 15 µg /day plus ribavirin 800-1200 mg daily. In patients with an early virological response (EVR), the dose of CIFN was reduced to 15 µg thrice a week for further 36 weeks. Patients with delayed virological response continued to receive daily CIFN plus ribavirin to complete 48 weeks. The patients were considered "non-responders" if there were less than 2 log reduction in HCV RNA at 12 weeks and detectable HCV RNA at 24 weeks. RESULTS: Twenty-four patients (55%) were non-responders and 20 patients were relapers to the previous treatment with pegylated interferon plus ribavirin (mean age 43.6 ± 9.4 years, males 25 (57%)). Nine patients were clinically cirrhotic (Child A). End of treatment virological response was achieved in 19 (43.1%) patients and sustained virological response (SVR) occurred in 12 (27.3%). Out of these 12 patients, eight were non-responders and four were relapers to the previous treatment. Advanced fibrosis or clinical cirrhosis was associated with low SVR. Adverse events were fever, myalgia, anorexia, depression, and weight loss. Two patients received granulocyte colony stimulating factor for transient neutropenia. Seven patients were given erythropoietin to improve hemoglobin, and six were treated for mild depression. Two patients developed portosystemic encephalopathy. CONCLUSIONS: More than one-quarter of treatment-experienced patients with HCV genotype 3 achieved SVR after re-treatment with consensus interferon plus ribavirin.

Hepatitis C virus (HCV) infection affects about 160 million people worldwide. Currently, it is treated with pegylated interferon (PEG-IFN) plus ribavirin, associated with a protease inhibitor in case of genotype 1 infection. However, this combination is often contraindicated and associated with severe adverse events that limit its use in clinical practice. Several drugs active against HCV are in an advanced phase of clinical development. Among these, sofosbuvir appears one of the most promising candidates for use in association with both interferon and interferon-free combinations. This review focuses on the results of several sofosbuvir-based phase III trials that have very recently become available. These studies show the administration of sofosbuvir associated with PEG-IFN and ribavirin for 12 weeks is associated with a very high rate of sustained virological responses (SVR) (about 90%) in naïve patients with genotypes 1, 4, 5 or 6. In patients infected by genotypes 2 or 3, the interferon-free combination of sofosbuvir and ribavirin administered for 12 weeks is associated with a SVR of 97% and 56% in naïve patients, and of 86% and 30% in experienced genotype 2 or 3 patients, respectively. The safety and tolerability profile is optimal and consistent with that of the other drugs administered in the combination (ribavirin and/or interferon). In conclusion, the recent phase III trials of sofosbuvir confirm the excellent results of phase II studies in terms of efficacy and safety and will probably open a new era in the fight against HCV.

Effect of caffeine-containing beverage consumption on serum alanine aminotransferase levels in patients with chronic hepatitis C virus infection: a hospital-based cohort study.


INTRODUCTION: To date, there have been no prospective studies examining the effect of coffee consumption on serum alanine aminotransferase (ALT) level among individuals infected with the hepatitis C virus (HCV). We conducted a hospital-based cohort study among patients with chronic HCV infection to assess an association between baseline coffee consumption and subsequent ALT levels for 12 months. MATERIALS AND METHODS: From 1 August 2005 to 31 July 2006, total 376 HCV-RNA positive patients were recruited. A baseline questionnaire elicited information on the frequency of coffee consumption and other caffeine-containing beverages. ALT level as a study outcome was followed through the patients' medical records during 12 months. The association between baseline beverage consumption and subsequent ALT levels was evaluated separately among patients with baseline ALT levels within normal range (≤45 IU/L) and among those with higher ALT levels (>45 IU/L). RESULTS: Among 229 patients with baseline ALT levels within normal range, 186 (81%) retained normal ALT levels at 12 months after recruitment. Daily drinkers of filtered coffee were three times more likely to preserve a normal ALT level than non-drinkers (OR=2.74; P=0.037). However, decaffeinated coffee drinkers had a somewhat inverse effect for sustained normal ALT levels, with marginal significance (OR=0.26; P=0.076). In addition, among 147 patients with higher baseline ALT levels, 39 patients (27%) had ALT reductions of ≥20 IU/L at 12 months after recruitment. Daily drinkers of filtered coffee had a significantly increased OR for ALT reduction (OR=3.79; P=0.034). However, in decaffeinated coffee drinkers, OR could not be calculated because no patients had ALT reduction. CONCLUSION: Among patients with chronic HCV infection, daily consumption of filtered coffee may have a beneficial effect on the stabilization of ALT levels.
The End-of-Treatment Ribavirin Concentration Predicts Hepatitis C Virus Relapse.

BACKGROUND: The optimization of combination therapy with ribavirin (RBV) and pegylated interferon alpha has substantially improved sustained virologic response (SVR) rates and lowered virologic relapse rates in patients infected with hepatitis C virus (HCV). In this study, we performed an analysis of the relationship between the end-of-treatment plasma RBV concentration and virologic relapse. METHODS: Thirty-four patients with HCV treated with pegylated interferon/RBV and with an end-of-treatment response were assayed for plasma RBV concentration using liquid chromatography assay coupled to tandem mass-spectrometric detection on the last day of the treatment. Clinical data and the concentration of RBV were compared between patients classified as either relapsers or nonrelapsers. RESULTS: Eleven patients (32.4%) relapsed and 23 patients (67.6%) achieved an SVR. The mean plasma RBV concentration on the last day of treatment was 1380 ± 312 ng/mL for relapsers and 2278 ± 569 ng/mL for SVR patients (P < 0.0001). A receiver operating characteristic analysis showed that a threshold of 1960 ng/mL was associated with the greatest sensitivity and specificity (100% and 83%, respectively, with an area under the curve of 0.94; P < 0.0001) for discriminating between patients who relapsed and those who did not. A univariate logistic regression analysis indicated that a plasma RBV concentration of <1960 ng/mL at the end of the treatment was strongly associated with relapse (odds ratio, 55; 95% confidence interval, 7.24-∞; P = 0.0001) independently of age, body weight, RBV dose, baseline viral load, the interleukin-28B genotype, and response to previous courses of treatment. CONCLUSIONS: Our study results highlight the relevance of measuring plasma RBV concentrations during and at the end of HCV treatment, with a view to avoiding virologic relapse.


BACKGROUND: Treatment for CH-C contains interferon with substantial associated side effects and health-related quality of life (HRQL) impairment. Currently, there is no published data assessing the impact of interferon-free regimens on HRQL. AIM: To report the HRQL of patients who participated in clinical trials of sofosbuvir (SOF) for CH-C. METHODS: CH-C patients were treated with sofosbuvir (SOF), pegylated interferon (PEG-IFN), ribavirin (RBV), or placebo in different combinations and duration (POSITRON, FISSION, FUSION, and NEUTRINO phase III trials). HRQL was assessed using SF- 36 at baseline, during, at the end of treatment, and at follow-up, and compared between treatment arms. RESULTS: HRQL scores decreased over the course of treatment for all treatment arms in all studies; however, patients returned to their baseline score by the end of follow-up. Compared to placebo, SOF and RBV was not associated with HRQL impairment (POSITRON). Compared to SOF and RBV, HRQL was significantly more impaired in the PEG-IFN and RBV arm (FISSION). For those treated with SOF and RBV, there was no difference in HRQL between 12 weeks or 16 weeks of
treatment (FUSION). Multivariate analysis demonstrated that depression, fatigue, and insomnia were important predictors of patients' HRQL prior, during or after treatment. Additionally, anemia and receiving interferon were predictors of HRQL impairment during treatment. Achieving sustained virologic response after 12 weeks of follow-up (SVR-12) with SOF and RBV was associated with improvement in HRQL scores from baseline. CONCLUSIONS: Treatment-related HRQL impairment during SOF and RBV regimen is mild, and does not increase with longer treatment duration. Achieving SVR-12 with SOF and RBV is associated with an improvement in HRQL.


BACKGROUND: Advances in hepatitis C virus (HCV) treatment have yielded improved virological response rates, and yet, many individuals with psychiatric illness still fail to receive HCV therapy. Concerns about safety, adherence, and efficacy of HCV treatment are compounded and treatment is further deferred when substance use is also present. This is especially problematic given the disproportionately high rates of both mental health issues and substance use among individuals living with HCV. OBJECTIVE: This study sought to examine HCV treatment outcomes in clients with serious mental illness (SMI) and with high rates of active substance use who were participating in a community-based HCV treatment program. PATIENTS AND METHODS: A retrospective chart review of 129 clients was carried out. Patients were classified as having an SMI if they had a history of bipolar disorder, psychotic disorder, past suicide attempt or mental health related hospitalization. RESULTS: Fifty-one patients were defined as having an SMI. Among the 46 patients with SMI and a detectable HCV viral load, HCV antiviral therapy was initiated in nine (19.6%). A relapse or an increase in substance use was common (77.8% or n=7), as was the requirement for adjustment or initiation of psychotropic medications (66.7% or n=6) during HCV antiviral therapy. Despite these barriers, rates of adherence to antiviral therapy were high and overall sustained virological response rates were comparable with published trials. CONCLUSION: This study is the first to report HCV treatment outcomes in a population in which SMI and active polysubstance use was prevalent and suggests that with appropriate models of care, clients with trimorbidity can be treated safely and effectively.


BACKGROUND: The development of thyroid antibodies and the alteration of thyroid function are the most common disorders associated with interferon alfa therapy in individuals with chronic hepatitis C (CHC). In this study, we compared the course of Graves disease (GD) between patients diagnosed with CHC and treated with interferon alfa and uninfected patients. METHODS: We retrospectively analyzed data from 39 GD patients (15 men and 24 women, group 1) affected by CHC and treated with interferon alfa and from 43 uninfected GD patients (19 men and 24 women, group 2) who were seen at our institution from 1999 to 2011. All GD patients were treated with methimazole (MMI). Daily dose of MMI, duration of MMI therapy,
RESULTS: The daily dose of MMI was found to be lower in group 1 as compared with group 2 (9.74 ± 5.94 mg/d vs 14.12 ± 8.64 mg/d in group 1 vs group 2, respectively, P < 0.01). In addition, the duration of MMI treatment was found to be lower in group 1 as compared with group 2 (13.98 ± 13.0 months vs 38.86 ± 27.13 months in group 1 vs group 2, respectively; P < 0.01). The remission rate from GD was higher in the patients of group 1 in comparison with the patients of group 2 (87.17 % vs 48.86% in group 1 vs group 2, respectively, P < 0.005).

CONCLUSION: Altogether, our data demonstrate a more favorable course of GD in the patients with CHC treated with interferon alfa compared with GD occurring in the patients without CHC.


OBJECTIVE: To conduct a systematic review and meta-analysis evaluating the efficacy and safety of antidepressant medications for the prevention of interferon-alpha (INF-α)-associated depression in patients with chronic hepatitis C virus (HCV). DATA SOURCES: Medline, Cochrane Central and PsycInfo from inception to September 2012, without limitations using terms describing hepatitis C and the individual drug names. STUDY SELECTION: We reviewed 132 citations for inclusion using the following criteria: randomised controlled trials in patients with chronic HCV initiating INF-α comparing prophylactic use of an antidepressant vs. placebo and reporting at least one outcome of interest [depression, completion of antiviral therapy, sustained virologic response (SVR), and serious adverse events and bleeding]. DATA EXTRACTION: Trial characteristics, assessment of risk of bias and data needed for analyses were extracted by two independent investigators using a standard extraction form. Disagreements were reviewed by a third investigator. RESULTS: A DerSimonian and Laird random-effects model was used for analysis. Heterogeneity and publication bias were evaluated where applicable. Of the seven included trials, the risk of bias was low in four and unclear in the remaining three. All trials evaluated selective serotonin reuptake inhibitors (SSRIs). Prophylactic use of a SSRI significantly reduced the risk of depression by 41% compared with placebo [RR, relative risk 0.59 (0.37-0.93)]. The impact of SSRIs on completion of antiviral therapy, SVR and serious adverse events was not found to be significant. CONCLUSIONS: SSRIs prevent depression in patients with HCV treated with INF-α therapy. The impact of SSRIs on completion of antiviral therapy or on the development of adverse events is less clear.


BACKGROUND & AIMS: We performed an open-label, multi-center, Phase 3 study of the safety and efficacy of twice-daily telaprevir in treatment-naive patients with chronic hepatitis C virus (HCV) genotype 1 infection, including those with cirrhosis. METHODS: Patients were randomly assigned to groups given telaprevir 1125 mg twice-daily or 750 mg every 8 hrs, plus peg-interferon alfa-2a and ribavirin for 12 weeks; patients were then given peg-interferon alfa-2a
and ribavirin alone for 12 weeks if their week 4 level of HCV RNA was <25 IU/mL, or for 36 weeks if their level was higher. The primary objective was noninferiority of telaprevir twice-daily vs every 8 hrs in producing a sustained virologic response 12 weeks after the end of therapy (SVR12) (based on a -11% lower limit of the 95% lower confidence interval for the difference between groups). **RESULTS:** At baseline, of 740 patients, 85% had levels of HCV RNA ≥800,000 IU/mL, 28% had fibrosis (F3–4), 14% had cirrhosis (F4), 57% were infected with HCV genotype 1a, and 71% had the non-CC IL28B genotype. Of patients who received telaprevir twice-daily, 74.3% achieved SVR12, compared with 72.8% of patients who received telaprevir every 8 hrs (difference in response, 1.5%; 95% confidence interval, -4.9% to 12.0%), so telaprevir twice-daily is noninferior to telaprevir every 8 hrs. All subgroups of patients who received telaprevir twice-daily vs those who received it every 8 hrs had similar rates of SVR12. Most frequent adverse events (AEs) in the telaprevir phase were fatigue (47%), pruritus (43%), anemia (42%), nausea (37%), rash (35%), and headache (26%); serious AEs were reported in 9% of patients. Rates of AEs and serious AEs were similar or slightly higher among patients receiving telaprevir every 8 hrs. **CONCLUSIONS:** Based on a phase 3 trial, telaprevir twice-daily is noninferior to every 8 hrs in producing SVR12, with similar levels of safety and tolerability. These results support use of telaprevir twice-daily in patients with chronic HCV genotype 1 infection, including those with cirrhosis. ClinicalTrials.gov number: NCT01241760.


**BACKGROUND:** Hepatitis C virus (HCV) infection is a serious disease worldwide and it leads to several serious hepatic sequels. Some studies find possible correlation between HCV and ischemic heart disease in retrospective observations. Based on lacked community-based evidence, the study aims to assess correlation between ischemic heart disease and chronic HCV infection via electrocardiogram (ECG) because its abnormalities is strongly associating with cardiovascular disease mortality. **METHODS:** The population was from one community health examination in December 2010 in a southern village of Taiwan. A total of 9856 participants were evaluated and finally 5015 eligible residents with age older than 40 years were included. The baseline characteristics and laboratory data in nonischemic ECG and ischemic ECG groups were compared, and multivariate-adjusted analysis was used to evaluate the risks to ischemic ECG. **RESULTS:** The higher prevalence of hypertension, metabolic syndrome and even HCV infection (25.3% versus 11.6%; P < 0.001) in ischemic ECG group than those in nonischemic ECG group. In the multivariate adjusted analysis, HCV infection would lead to a 1.759-fold risk to ischemic ECG when compared with non-HCV subjects. **CONCLUSIONS:** HCV was strongly associated with ischemic ECG findings in this community study, and it could be a nonconventional risk factor for coronary artery disease.

A new class of highly potent NS5A inhibitors with an unsymmetric benzimidazole-difluorofluorene-imidazole core and distal [2.2.1]azabicyclic ring system was discovered. Optimization of antiviral potency and pharmacokinetics led to the identification of 39 (ledipasvir, GS-5885). Compound 39 (GT1a replicon EC50 = 31 pM) has an extended plasma half-life of 37-45 hours in healthy volunteers, and produces a rapid > 3 log10 viral load reduction in monotherapy at oral doses of 3 milligrams or greater with once-daily dosing in genotype 1a HCV infected patients. 39 has been shown to be safe and efficacious with SVR12 rates up to 100% when used in combination with direct-acting antivirals having complementary mechanisms.


BACKGROUND. Hepatitis C virus (HCV) is spread through direct contact with blood, although alternative routes of transmission may contribute to the global burden. Perinatal infection occurs in up to 5% of HCV-infected mothers, and presence of HCV RNA in breast milk has been reported. We investigated the influence of breast milk on HCV infectiousness. METHODS/RESULTS. Human breast milk reduced HCV infectivity in a dose-dependent manner. This effect was species-specific because milk from various animals did not inhibit HCV infection. Treatment of HCV with human breast milk did not compromise integrity of viral RNA or capsids but destroyed the lipid envelope. Fractionation of breast milk revealed that the antiviral activity is present in the cream fraction containing the fat. Proteolytic digestion of milk proteins had no influence on its antiviral activity, whereas prolonged storage at 4°C increased antiviral activity. Notably, pretreatment with a lipase inhibitor ablated the antiviral activity and specific free fatty acids of breast milk were antiviral. CONCLUSIONS. The antiviral activity of breast milk is linked to endogenous lipase-dependent generation of free fatty acids, which destroy the viral lipid envelope. Therefore, nursing by HCV-positive mothers is unlikely to play a major role in vertical transmission.


BACKGROUND: A substantial proportion of hepatitis C virus (HCV)-1b infected patients do not response to pegylated interferon-α plus ribavirin (PegIFNα/RBV) combination therapy that
was partially associated with mutations in the non-structural 5A (NS5A) protein.

**OBJECTIVES:** Analysis of NS5A polymorphisms in HCV genotype 1b pre-treatment serum samples from Estonian patients and their effect on the treatment response. **PATIENTS AND METHODS:** Twenty-nine complete NS5A sequences obtained from patients with chronic HCV-1b infection who had received combined therapy with PegIFNα-2a/RBV were analyzed and compared with the prototype strain HCV-J. Twelve patients achieved a sustained virological response (SVR), 15 were non-SVR and 2 patients stopped treatment because of side effects.

**RESULTS:** No significant difference in total number of amino acid mutations was observed between isolates from SVR and non-SVR patients in any known regions of the NS5A protein. However, specific amino acid substitutions at positions 1989 and 2283 correlated significantly with SVR, mutations at positions 1979, 2107, 2171 and 2382 were associated with non-response to treatment and amino acid substitution at position 2319 was observed in relapsers. At phylogenetic analysis, NS5A nucleotide sequences have been subdivided into four groups characterized by the different treatment response. Twenty-four novel nucleotide polymorphisms and 11 novel amino acid polymorphisms were identified based on the phylogenetic tree topology. **CONCLUSIONS:** Specific amino acid substitutions correlating with the treatment response were found. Polymorphisms revealed by phylogenetic analysis may define the signature patterns for treatment susceptible and treatment resistant strains prevalent in Estonia.


Multiple genotype 1a clones have been reported, including the very first hepatitis C virus (HCV) clone called H77. The replication ability of some of these clones has been confirmed in vitro and in vivo, although this ability is somehow compromised. We now report a newly isolated genotype 1a clone, designated HCV-RMT, which has the ability to replicate efficiently in patients, chimeric mice with humanized liver, and cultured cells. An authentic subgenomic replicon cell line was established from the HCV-RMT sequence with spontaneous introduction of three adaptive mutations, which were later confirmed to be responsible for efficient replication in HuH-7 cells as both subgenomic replicon RNA and viral genome RNA. Following transfection, the HCV-RMT RNA genome with three adaptive mutations was maintained for more than 2 months in HuH-7 cells. One clone selected from the transfected cells had a high copy number, and its supernatant could infect naïve HuH-7 cells. Direct injection of wild-type HCV-RMT RNA into the liver of chimeric mice with humanized liver resulted in vigorous replication, similar to inoculation with the parental patient’s serum. A study of virus replication using HCV-RMT derivatives with various combinations of adaptive mutations revealed a clear inversely proportional relationship between in vitro and in vivo replication abilities. Thus, we suggest that HCV-RMT and its derivatives are important tools for HCV genotype 1a research and for determining the mechanism of HCV replication in vitro and in vivo.


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**BACKGROUND:** Pre-treatment identification of patients likely to achieve a sustained virological response (SVR) with peginterferon alfa-2a/ribavirin would be useful for individualizing treatment choices. **AIMS:** Devise a simple scoring system to identify patients with high probability of achieving an SVR with peginterferon alfa-2a/ribavirin. **METHODS:** Using data from 2109 Caucasian treatment-naive HCV genotype 1 mono-infected patients from the PROPHESYS cohorts, the relationship between favourable baseline characteristics and SVR was explored using generalized additive model analysis, and a scoring system was devised to predict SVR. **RESULTS:** Points were assigned for: age (years) (≤35: 2; >35, ≤45: 1; >45: 0); body mass index (kg/m²) (≤20: 2; >20, ≤22: 1; >22: 0); HCV RNA (IU/ml) (≤100000: 3; >100000-400000: 2; >400000-800000: 1; >800000: 0); platelets (>150 x 10⁹/l: 1; ≤150 x 10⁹/l: 0); ALT (x upper limit of normal [ULN]) (>3: 1; ≤3: 0); AST (x ULN) (≤1: 1; >1: 0). 1029, 698 and 382 patients had scores of 0-2, 3-4, and ≥5, respectively, among whom SVR rates were 35.0%, 54.9% and 76.7%. SVR in patients with scores ≥5 and undetectable HCV RNA by Week 4 was 86.7%. The score was tested against two databases of patients who received peginterferon alfa-2a/ribavirin in other clinical trials; similar high SVR rates in patients with scores ≥5 were reported. **CONCLUSIONS:** The scoring system can reliably identify treatment-naive HCV genotype 1 mono-infected Caucasian patients who have a high probability of achieving an SVR with peginterferon alfa-2a/ribavirin and will be particularly useful where protease inhibitors are not readily available.


Coinfection of hepatitis B virus (HBV) with hepatitis C virus (HCV) is quite common, leading to an increase in morbidity and mortality. As such, HBV vaccination is recommended in HCV-infected individuals. However, HBV vaccine responses in HCV-infected individuals are often blunted compared with uninfected populations. The mechanism for this failure of vaccine response in HCV-infected subjects remains unclear. In this study, we investigated the expression and function of an inhibitory receptor, killer cell lectin-like receptor subfamily G member 1 (KLRG1), in the regulation of CD4⁺ T cells and HBV vaccine responses during HCV infection. We demonstrated that KLRG1 was overexpressed on CD4⁺ T cells from HCV-infected, HBV vaccine nonresponders compared with HBV vaccine responders. The capacity of CD4⁺ T cells to proliferate and secrete IL-2 cytokine was inversely associated with the level of KLRG1 expression. Importantly, blocking KLRG1 signaling resulted in a significant improvement in CD4⁺ T cell proliferation and IL-2 production in HCV-infected, HBV vaccine nonresponders in response to TCR stimulation. Moreover, blockade of KLRG1 increased the phosphorylation of Akt (Ser⁴⁷³) and decreased the expression of cell cycle inhibitors p16ink4a and p27kip1, which subsequently enhanced the expression of cyclin-dependent kinase 2 and cyclin E. These results suggest that the KLRG1 pathway impairs CD4⁺ T cell responses to neoantigen and induces a state of immune senescence in individuals with HCV infection, raising the possibility that blocking this negative-signaling pathway might improve HBV vaccine responses in the setting of chronic viral infection.

Enrichment of viruses is essential for making high dose viral stocks for vaccines and virus-related research. Since the widely used ultracentrifugation for concentrating viral stock requires ultra-high speed rotation, it easily destroys the activity of some viruses, for instance, hepatitis c virus (HCV), which has a fragile structure and low virus titer. We introduce a novel method to concentrate HCV virus in stock by using a hierarchically self-organized monolithic nanoporous membrane made by stepwise anodization. The pores at the top part of the membrane have very regular sizes that are suitable for the perfect filtration of the virus particles in the stock. On the other hand, the remaining part has large pores that maintain high flux and mechanical strength of the membrane under the high pressure (up to 10 bar). The enrichment efficiency of HCV in crude stocks by using the membrane became over 91%, which is four times higher than that (∼22%) obtained by conventionally used centrifugation. A very high efficiency results from the perfect filtration and no damage to the virion particles during the enrichment process, whereas significant damage to the HCV occurs during centrifugation. The hierarchically self-organized monolithic nanoporous membrane could be effectively employed for concentrating various fragile viruses in stocks, for instance, rabies virus and human immunodeficiency virus in addition to HCV virus.

HIV/HCV COINFECTION


BACKGROUND: HIV and hepatitis C virus (HCV) infections may increase interleukin-6 (IL-6) and C-reactive protein (CRP). However, relationships between inflammatory biomarkers, chronic viral infections, clinical factors, and behavioral factors remain poorly understood.

METHODS: Using linear regression, we modeled cross-sectional associations between loge IL-6 or loge CRP levels and HCV, HIV, injection drug use, and comorbidity among 1191 injection drug users. RESULTS: Mean age was 47 years, 46.0% reported currently injecting drugs, 59.0% were HCV mono-infected, and 27% were HCV/HIV co-infected. In multivariable models, higher loge IL-6 was associated with HCV mono-infection [β = 0.191, 95% confidence interval (CI): 0.043 to 0.339] and HCV/HIV co-infection (β = 0.394, 95% CI: 0.214 to 0.574). In contrast, HCV mono-infection (β = -0.523, 95% CI: -0.275 to -0.789) and HCV/HIV co-infection (β = -0.554 95% CI: -0.260 to -0.847) were associated with lower CRP. Lower CRP with HCV infection was independent of liver fibrosis severity, synthetic function, or liver injury markers; CRP decreased with higher HCV RNA. Increased injection intensity was associated with higher IL-6 (P = 0.003) and CRP (P < 0.001); increasing comorbidity (P < 0.001) and older age (P = 0.028) were associated with higher IL-6; older age was associated with higher CRP among HCV-uninfected participants (P = 0.021). CONCLUSION: HIV and HCV infections contribute to chronic inflammation; however, reduced CRP possibly occurs through HCV-mediated mechanisms. Findings highlight potentially modifiable contributors to inflammation.

OBJECTIVE: To assess the ability of the cirrhosis risk score (CRS) to predict liver fibrosis progression in HIV/hepatitis C virus (HCV)-coinfected patients. DESIGN: Retrospective follow-up study. METHODS: Based on a minimum follow-up time of 10 years with HCV infection, 190 HIV/HCV-coinfected patients were classified according to their METAVIR score: (1) 25 nonprogressor patients who did not develop fibrosis (F0) and (2) 165 progressor patients who developed fibrosis (F ≥ 1). Seven polymorphisms of CRS signature and IL28B genotype were performed using the GoldenGate assay. The CRS signature was calculated by naive Bayes formula as previously described. RESULTS: Nonprogressors had CRS values significantly lower than progressors (0.61 versus 0.67; P = 0.043). Among the progressors, we observed similar CRS values through all the fibrosis stages (F1/F2/F3/F4). The percentage of patients with CRS > 0.70 (high risk of developing fibrosis) was higher in progressors than in nonprogressors; but the percentages with values between 0.50 and 0.70 (intermediate risk) and <0.50 (low risk) were quite similar for each of the fibrosis stages (P = 0.047). The area under the receiver-operating characteristic curve of CRS for discriminating nonprogressor versus progressor was 0.625 (P = 0.043). When clinical variables were considered (age at HCV infection, intravenous drug use, gender, IL28B, and HCV genotype), the area under the receiver-operating characteristic curve of CRS improved up to 0.739 (P < 0.001). CONCLUSIONS: CRS itself seems not to be a good marker for identifying HIV/HCV-coinfected patients who are at high risk of developing liver fibrosis. However, CRS score coupled with clinical factors might help to distinguish between nonprogressors and progressors patients.


BACKGROUND. There is an international epidemic of hepatitis C virus (HCV) infection among human immunodeficiency virus (HIV)-infected men who have sex with men. Sustained virologic response (SVR) rates with pegylated interferon and ribavirin treatment are higher in these men during acute HCV than during chronic HCV, but treatment is still lengthy and SVR rates are suboptimal. METHODS. We performed a pilot study of combination therapy with telaprevir, pegylated interferon, and ribavirin in acute genotype 1 HCV infection in HIV-infected men. Men who were treated prior to the availability of, or ineligible for, telaprevir were the comparator group. The primary endpoint was SVR12, defined as an HCV RNA level <5IU/mL at least 12 weeks after completing treatment. RESULTS. In the telaprevir group, 84% (16/19) achieved SVR 12 versus 63% (30/48) in the comparator group. Among men with SVR, median time to undetectable viral load was week 2 in the telaprevir group vs week 4 in the comparator group, and 94% vs 53% had undetectable viral loads at week 4. Most patients (81%) who achieved SVR in the telaprevir group received ≤12 weeks of treatment and there were no relapses after treatment. The overall safety profile was similar to that known for telaprevir-based
regimens. **CONCLUSIONS.** Incorporating telaprevir into treatment of acute genotype 1 HCV in HIV-infected men halved the treatment duration and increased the SVR rate. Larger studies should be done to confirm these findings. Clinicians should be alert to detect acute HCV infection of HIV-infected men to take advantage of this effective therapy and decrease further transmission in this epidemic.


**PURPOSE:** Our aim was to explore the interplay between human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections in the expression of cognitive disorders. **METHODS:** We performed a multi-centre cross-sectional study, enrolling three groups of asymptomatic outpatients matched for age and education: (1) HIV mono-infected; (2) HCV mono-infected; (3) HIV-HCV co-infected. All subjects were subjected to the Zung depression scale and a comprehensive neuropsychological battery. **RESULTS:** A total of 50 patients for each group were enrolled. Patients in the three groups did not significantly differ in the main common demographic and clinical characteristics, except for a lower proportion of past injecting drug use (IDU) in group 1 (4 %) in comparison to groups 2 (38 %, p < 0.001) and 3 (78 %, p < 0.001), a longer duration of HIV infection in group 3 in comparison to group 1 (p < 0.001) and a longer duration of HCV infection in group 3 in comparison to group 2 (p = 0.028). Overall, 39.3 % of patients showed minor cognitive impairment, with a higher proportion in group 3 (54 %) when compared to groups 1 (28 %, p = 0.015) or 2 (36 %, p = 0.108). Patients in group 3 [odds ratio (OR) 3.35, p = 0.038 when compared to group 1] and those with higher depression scores (OR 1.05, p = 0.017) showed an increased risk of cognitive impairment after adjusting for education and past injection drug use. In particular, group 3 showed worse performance in psychomotor speed tasks when compared to group 1 (p = 0.033). **CONCLUSIONS:** A worse cognitive performance in HIV-HCV co-infected patients was observed, suggesting an additive role of the two viruses in the pathogenesis of cognitive disorders.


Osteoporosis is increasingly reported in the aging HIV-positive population, and co-infection with hepatitis C virus (HCV) may further increase the risk of osteoporosis. However, it remains unclear whether HCV-related increased fracture risk is a function of the severity of liver disease. We calculated the time-updated alanine aminotransferase to platelet ratio index (APRI) score (an indirect marker of hepatic fibrosis) in all HIV-infected patients enrolled in the Veterans Affairs' Clinical Case Registry between 1984 and 2009. The association between HCV co-infection and incident osteoporotic fracture (defined as closed wrist, vertebral, or hip fracture) was assessed in univariate and multivariate Cox survival models adjusting for traditional risk factors for osteoporosis and APRI score or the presence of cirrhosis. A total of 772 osteoporotic fractures were identified among 56,660 HIV-infected patients (98.1% male; 31.3% HCV co-infected; median age 44.0 years) contributing 305,237 patient-years of follow-up. Fracture rates were
significantly higher among HIV/HCV patients than HIV-only patients (2.57 versus 2.07/1000 patient-years, relative risk = 1.24, p < 0.0001). In a Cox multivariable model including age, race, smoking, drug use, body mass index, and antiretroviral therapy, HCV co-infection remained an independent predictor of osteoporotic fractures after controlling for presence of cirrhosis (hazard ratio [HR] = 1.32; p < 0.001) or APRI score (HR = 1.30; p = 0.003). Among HIV/HCV co-infected patients, cirrhosis strongly predicted osteoporotic fractures (HR = 1.65; 95% confidence interval [CI] 1.11-2.44; p = 0.012), but APRI score was a weaker predictor (HR = 1.008; 95% CI 1.002-1.014; p = 0.015). **In conclusion**, among HIV-infected patients, severity of liver disease partly explains the HCV-associated increased risk of osteoporotic fractures. Other determinants of this increased risk remain to be defined. © 2013 American Society for Bone and Mineral Research.


Chronic HCV infection affects 130-170 million individuals worldwide and there are currently 34 million people living with HIV/AIDS. The aim of treatment of HCV is the elimination of the virus (sustained virological response). With development of drugs that specifically target HCV replication, direct-acting agents, sustained virological response rates have dramatically changed for genotype 1 infections. Challenges in the use of direct-acting agents in patients with HIV/HCV co-infection include the potential for drug-drug interactions between HIV and HCV drugs, additional drug toxicities and the need for therapy with IFN-α. Faldaprevir (FDV), previously known as BI 201335, is a second-wave HCV NS3/4A protease inhibitor with highly potent in vitro activity against HCV GT-1a/1b and improved pharmacokinetics suitable for once-daily dosing. FDV is currently in Phase III development. This article will review the pharmacology and pharmacodynamics of FDV, the efficacy and safety of the drug and explore possible future developments in the management of chronic hepatitis C infection, focusing on HIV/HCV co-infected patients.


Boceprevir and telaprevir are 2 specific inhibitor of the hepatitis C (HCV) serine protease 3. Cutaneous side effects have been reported with high frequency, essentially rash and dry skin. We report a case of drug rash with eosinophilia and systemic symptoms (DRESS) due to boceprevir. A 56-year-old African woman with chronic hepatitis C complicated of cirrhosis and cryoglobulinemia received the association of pegylated interferon alfa-2a (peg-1NF) and ribavirin (RBV) for 4 weeks then the addition of Boceprevir. She was also co-infected with HIV state A2. Eight weeks after the addition of Boceprevir she developed a generalized maculopapular exanthema with fever, facial oedema, apparition of lymph node and alteration of the general state. She presented an eosinophilia (up to 3.0X109 cells/l), no biological inflammatory syndrome. The computed tomography revealed several lymph nodes located in the abdominal and inguinal areas. The cutaneous biopsy was consistent with a drug rash reaction. The HCV treatment was stopped and the patient was treated with topical steroids. Cutaneous and systemic symptoms
disappeared in few weeks. Boceprevir was considered the culprit drug. We report to our knowledge the first case of DRESS due to boceprevir.

**Biopsychosocial factors associated with pain in veterans with the hepatitis C virus.**

Little research has examined etiological factors associated with pain in patients with the hepatitis C virus (HCV). The purpose of this study was to evaluate the relationship between biopsychosocial factors and pain among patients with HCV. Patients with HCV and pain (n = 119) completed self-report measures of pain, mental health functioning, pain-specific psychosocial variables (pain catastrophizing, self-efficacy for managing pain, social support), prescription opioid use, and demographic characteristics. In multivariate models, biopsychosocial factors accounted for 37% of the variance in pain severity and 56% of the variance in pain interference. In adjusted models, factors associated with pain severity include pain catastrophizing and social support, whereas variables associated with pain interference were age, pain intensity, prescription opioid use, and chronic pain self-efficacy (all p values <0.05). The results provide empirical support for incorporating the biopsychosocial model in evaluating and treating chronic pain in patients with HCV.

**Inhibitio of Hepatitis C Virus Replication In Vitro by Xanthohumol, A Natural Product Present in Hops.** Lou S1, Zheng YM2, Liu SL2, Qiu J3, Han Q1, Li N1, Zhu Q1, Zhang P1, Yang C1, Liu Z1. Planta Med. 2013 Dec 19. [Epub ahead of print].

Hepatitis C virus is a major cause of chronic liver disease worldwide. Xanthohumol, a prenylated flavonoid from hops, has various biological activities including an antiviral effect. It was previously characterized as a compound that inhibits bovine viral diarrhea virus, a surrogate model of hepatitis C virus. In the present work, xanthohumol was examined for its ability to inhibit hepatitis C virus replication in a cell culture system carrying replicating hepatitis C virus RNA replicon. 0.2% DMSO and 500 units/mL interferon-alpha treatments were set as a negative and positive control, respectively. The inhibitory effect by xanthohumol was determined by the luciferase activity of the infected Huh7.5 cell lysates and the hepatitis C virus RNA levels in the culture. Xanthohumol at 3.53 µM significantly decreased the luciferase activity compared to the negative control (p < 0.01). Xanthohumol at 7.05 µM further decreased the luciferase activity compared to xanthohumol at 3.53 µM (p = 0.015). Xanthohumol at 7.05 µM or 14.11 µM achieved an inhibitory effect similar to that of interferon-alpha 2b (p > 0.05). Xanthohumol at 3.53 µM significantly reduced the hepatitis C virus RNA level compared to the negative control (p = 0.001). Although the results of xanthohumol at 7.05 µM had a higher variation, xanthohumol at the 7.05 µM and 14.11 µM decreased the hepatitis C virus RNA level to that achieved by interferon-alpha (p > 0.05). **In conclusion,** xanthohumol displays anti-hepatitis C virus activity in a cell culture system and may be potentially used as an alternative or complementary treatment against the hepatitis C virus.
Epidemiology, Diagnostics, and Miscellaneous Works


BACKGROUND & AIMS: Covert hepatic encephalopathy (CHE) impairs quality of life (QOL) and can be difficult to diagnose. Patient-administered methods that do not require specialized tests or equipment might increase rates of detection. We performed a longitudinal study to determine whether demographic data and responses to a validated QOL questionnaire, the Sickness Impact Profile (SIP), can identify patients with CHE. METHODS: Patients with cirrhosis without prior overt HE were recruited from outpatient liver clinics at Virginia Commonwealth University Medical Center, from August 2008 through February 2012. We performed cognitive tests on 170 patients (mean age, 55 y; mean model for end-stage liver disease score, 9; 50% with hepatitis C-associated and 11% with alcohol-associated cirrhosis). Patients were also given the SIP questionnaire (136 questions on 12 QOL topics, requiring a yes or no answer) at enrollment, 6 months, and 12 months. The proportion of patients that responded "yes" to each question was compared between those with and without CHE. Patient variables (non-cognitive), demographics (age, education, sex, alcoholic etiology), and SIP questions that produced different responses between groups were analyzed by logistic regression and receiver operating characteristic analyses. RESULTS: Based on cognitive test results, 93 patients (55%) had CHE when the study began. They had a higher proportion of "yes" responses to 54 questions on the SIP questionnaire, across all categories. We developed a formula to identify patients with CHE based on age, sex, and responses to 4 SIP questions (a SIP CHE score). Baseline SIP CHE scores >0 identified patients with CHE with 80% sensitivity and 79% specificity. Of the 98 patients that returned for the 6-month evaluation, 50% had CHE (the SIP CHE identified these with 88% sensitivity). Of the 50 patients that returned for the 12-month evaluation, 32% had CHE (the SIP CHE score identified these with 81% sensitivity). CONCLUSIONS: We developed a system to identify patients with CHE based on age, sex, and responses to 4 SIP questions; this formula identified patients with CHE with >80% sensitivity over a 12-month period after the initial enrollment. Patient-administered CHE screening strategies that do not include specialized tests could increase detection of CHE and improve therapy.


BACKGROUND The burden of hepatitis C (HCV) treatment is growing, as is the political resolve to tackle the epidemic. Primary care will need to work more closely with secondary care to succeed in reducing the prevalence of chronic HCV. Aim To identify research relating to the provision of antiviral treatment for HCV in primary care. Design and setting A narrative systematic review of six databases. METHOD Medline, Embase, Cinahl, PsycINFO, Web of Science, and Cochrane were searched. Relevant journals were searched by hand for articles to be included in the review. Reference lists of relevant papers were reviewed and full-text papers were retrieved for those deemed to potentially fulfil the inclusion criteria of the review.

Caring Ambassadors Program Hepatitis C Literature Review © 2014
RESULTS A total of 683 abstracts led to 77 full-text articles being retrieved, of which 16 were finally included in the review. An evidence base emerged, highlighting that community-based antiviral treatment provision is feasible and can result in clinical outcomes comparable to those achieved in hospital outpatient settings. Such provision can be in mainstream general practice, at community addiction centres, or in prisons. GPs must be trained before offering such a service and there is also a need for ongoing specialist supervision of primary care practice. Such training and supervision can be delivered by teleconference, although, even with such ready availability of training and supervision, only a minority of GPs are likely to want to provide antiviral treatment.

CONCLUSION There is emerging evidence supporting the effectiveness of antiviral treatment provision for patients with chronic hepatitis C in a wide variety of primary care and wider community settings. Training and ongoing supervision of primary care practitioners by specialists is a prerequisite. There is an opportunity through future research activity to evaluate typologies of patients who would be best served by primary care-based treatment and those for whom hospital-based outpatient treatment would be most appropriate.

Efficacy and safety of treatment of hepatitis C in patients with inflammatory bowel disease.

BACKGROUND & AIMS: There is uncertainty about the efficacy and safety of treatment for hepatitis C virus (HCV) infection in patients with inflammatory bowel disease (IBD). IBD can become exacerbated during treatment with interferon (IFN), and serious adverse events, such as pancytopenia or hepatotoxicity, can be compounded by drug interactions. We investigated the risk of exacerbation of IBD during HCV therapy and the rate of adverse effects of concomitant therapy for HCV and IBD. We also evaluated the efficacy of HCV treatment in the IBD population. METHODS: We conducted a retrospective review of all patients who underwent IFN-based treatment for HCV at the Mayo Clinic in Rochester, Minnesota from 2001 to 2012. Exacerbation of IBD was evaluated by clinical, endoscopic, and histologic parameters during antiviral therapy and the ensuing 12 months. Hematologic toxicity was assessed by levels of all 3 cell lineages at baseline and during therapy. Efficacy of antiviral treatment was assessed by serum levels of HCV RNA until 24 weeks after completion of therapy. We also conducted a detailed MEDLINE database search and reviewed the literature on this topic. RESULTS: We identified 15 subjects with concomitant IBD (8 with ulcerative colitis and 7 with Crohn's disease). Only 1 patient experienced exacerbation of the disease during therapy; symptoms were controlled with mesalamine enemas. Another patient developed a flare shortly after completing antiviral therapy; symptoms returned spontaneously to baseline 2 weeks later. All subjects experienced an anticipated degree of pancytopenia while on IFN-based therapy. The rate of sustained virologic response was 67%. A concise review of available literature regarding the safety and efficacy of HCV treatment in IBD patients is also presented; although limited, the published data appear to support the safety of treatment with IFN in patients whose IBD is under control. CONCLUSIONS: In conjunction with data from the literature, our findings indicate that the efficacy and safety of HCV therapy with IFN and ribavirin for patients with IBD are comparable to those of subjects without IBD.

Hepatitis C virus (HCV) induces insulin resistance, which improves upon viral clearance. Telaprevir is a protease inhibitor effective against HCV genotype 1. We report a case whose history suggests that telaprevir may induce some antidiabetic effect independently of its suppression of HCV. A 56-year-old woman with obesity, type 2 diabetes treated with sitagliptin and metformin, and HCV-related cirrhosis was given triple therapy with pegylated interferon-alpha, ribavirin, and telaprevir. After two weeks of treatment, HCV RNA was no longer detectable but the patient described a pronounced drop in the capillary glucose levels and episodes of hypoglycemia that compelled her to stop all antidiabetic treatment. One month after stopping telaprevir, she had to resume her antidiabetic treatment, despite a persisting virological response. Despite reaching a sustained virological response, her diabetes progressed. Although the suppression of HCV replication may have played a role in reducing glucose intolerance, the fact that this patient resumed her prior antidiabetic treatment upon completing the telaprevir treatment, while still aviremic, suggests that telaprevir may have an additional antidiabetic effect. Further evidence about the possible role and mechanisms of telaprevir as antidiabetic agent is warranted. This article is protected by copyright. All rights reserved.


BACKGROUND: Hepatitis C infection (HCV) among individuals aged 15-24 years has increased in Massachusetts, likely due to injection drug use. The prevalence of injection equipment sharing (sharing) and its association with age was examined in a cohort of out-of-treatment Massachusetts substance users. METHODS: This analysis included baseline data from a behavioral intervention with substance users. Younger and older (<25 versus >=25 years) injection drug users were compared on demographic characteristics, substance use practices, including factors present during the most recent sharing event ("event-level factors"), and HCV testing history. RESULTS: Sharing was reported by 41% of the 484 individuals who reported injection drug use in the past 30 days. Prevalence of sharing varied by age (50% <25 years old versus 38% >=25 years, p = 0.02). In a multivariable logistic regression model younger versus older individuals had twice the odds of sharing (95% CI = 1.26, 3.19). During their most recent sharing event, fewer younger individuals than older had their own drugs available (50% versus 75%, p < 0.001); other injection event-level factors did not vary by age. In the presence of PTSD, history of exchanging sex for money, or not being US born, prevalence of sharing by older users was higher and was similar to that of younger users, such that there was no association between age and sharing. CONCLUSIONS: In this cohort of injection drug users, younger age was associated with higher prevalence of sharing, but only in the absence of certain stressors. Harm reduction efforts might benefit from intervening on mental health and other stressors in addition to substance use. Study findings suggest a particular need to address the dangers of sharing with young individuals initiating injection drug use.

OBJECTIVES: Methamphetamine (MA) use has increased in the United States in the last 20 years and is a risk factor for hepatitis C virus (HCV) infection. The purpose of this study was to determine the characteristics and HCV infection outcomes of patients with a history of MA use. METHODS: Subjects consisted of newly entered patients in the Veterans Affairs (VA) HCV registry at a single VA medical center from January 1, 2004, to June 30, 2004, and from January 1, 2007, to June 30, 2007. Univariate and multivariate analyses related to HCV infection antiviral treatment outcomes through 2010 was performed. RESULTS: A total of 198 consecutive eligible HCV registry patients were analyzed, and 40% had a history of MA use. Of patients with MA use history, 46% (36/79) had active use (within 6 months) at initial contact. Active MA users were significantly younger (mean age, 45.5 years), with more concomitant drug use (86%), compared with patients without MA use (mean age, 53.5 years; 42% minority; 29% other drug use). Overall, 71% of the 198 patients reported a history of problematic alcohol use, and 47% of those reported active abuse. Logistic regression analyses indicated that MA use did not significantly adversely affect antiviral treatment initiation, completion, or sustained virological response rates compared with that in patients without MA use. Active alcohol users had lower treatment initiation than patients without alcohol use. CONCLUSIONS: MA use is common in recent US veterans with HCV infection and occurs in younger patients with polysubstance use. Prior history or active MA use does not seem to adversely affect HCV infection clinic treatment compared with that in HCV-infected patients without MA use.


CONTEXT: In 2012, the New York City Department of Health and Mental Hygiene matched HIV, tuberculosis, viral hepatitis, and sexually transmitted disease surveillance data to identify the burden of infection with multiple diseases. METHODS: HIV, tuberculosis, hepatitis B, hepatitis C, chlamydia, gonorrhea, and syphilis surveillance data from 2000 to 2010 were matched using a deterministic method. Data on deaths from the Department of Health and Mental Hygiene's Office of Vital Statistics were also matched. RESULTS: The final data set contained 840,248 people; 13% had 2 or more diseases. People with a report of syphilis had the highest proportion of matches with other diseases (64%), followed by gonorrhea (52%), HIV (31%), tuberculosis (23%), hepatitis C (20%), chlamydia (16%), and hepatitis B (11%). CONCLUSIONS: The findings indicate several possible infectious disease syndemics in New York City and highlight the need to integrate surveillance data from different infectious disease programs. Conducting the match brought surveillance programs together to work collaboratively and has resulted in ongoing partnerships on programmatic activities that address multiple diseases.


Antiviral therapy consisting of interferon-alpha and ribavirin for chronic hepatitis C infection is
associated with multi-system side-effects. Ophthalmologic complications are common and can be classified into two groups: interferon-associated retinopathy and atypical adverse events. Interferon-associated retinopathy has been investigated by multiple observational studies that have found widely divergent results. The clinical importance of this complication is, consequently, controversial. This review examines the literature with the specific goal of identifying the most important ophthalmologic issues facing the hepatologist prescribing antiviral therapy. Accordingly, it assesses the incidence of interferon-associated retinopathy, as well as its risk factors, pathogenesis, clinical manifestations and options for management using data from the observational studies. The likely benefit of a screening program, especially one targeting patients with the highest risk of developing interferon-associated retinopathy, is analysed. Atypical ophthalmologic adverse events occur less frequently than interferon-associated retinopathy during antiviral therapy for chronic hepatitis C infection. They often, however, lead to irreversible vision loss. We examine the reports of these adverse events - in individual case reports or case series and in the observational studies investigating interferon-associated retinopathy - to describe the spectrum of these adverse events, the likely outcome for patients and to highlight the most important areas of future clinical research.


Provision of hepatitis C virus (HCV) assessment and treatment via opioid substitution treatment (OST) clinics has been posed as an effective means of engaging populations with high HCV prevalence. This study explores OST client and health professional reports concerning barriers and facilitators affecting the delivery and uptake of HCV care and treatment within OST settings. In-depth interviews were conducted with 57 clients, 16 staff from four NSW clinics participating in the Australian ETHOS study and three peer workers. Client participants included those who had not had HCV assessment; those who had HCV assessment only; and those who were awaiting or undertaking HCV treatment. A clear difference in decisions about HCV treatment emerged between participant groups. For those who have not been assessed, barriers to engaging with HCV care included the perception that they were physically well, were not experiencing HCV symptoms, had other life priorities and were concerned about the side effects and tolerability of treatment. Those who had engaged with care expressed motivations stemming from seeing friends becoming unwell, wanting to live longer and hearing positive stories of treatment. For those interested in HCV treatment, issues related to both provider and setting were important, such as presence of an engaged clinician, an accessible treatment pathway and availability of support. In this integrated care model, some barriers to HCV care and treatment (particularly those relating to health provider and the system) are minimized. In this setting, HCV treatment remained an unattractive option for a significant number of clients. Providing ways for those without HCV symptoms to be assessed for liver damage may be important to open up alternative conversations about HCV care. Further, the importance of a changing discourse of treatment is apparent from these data and could be enhanced by peer communication that provides information about successful treatment experiences.

BACKGROUND: Antiviral therapy for recurrent hepatitis C infection after liver transplantation is controversial due to unresolved balance between benefits and harms. OBJECTIVES: To compare the therapeutic benefits and harms of different antiviral regimens in patients with hepatitis C re-infected grafts after liver transplantation. SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, 2013), MEDLINE, EMBASE, and Science Citation Index Expanded to February 2013. SELECTION CRITERIA: We considered only randomised clinical trials (irrespective of language, blinding, or publication status) comparing various antiviral therapies (alone or in combination) in the treatment of hepatitis C virus recurrence in liver transplantation for the review. DATA COLLECTION AND ANALYSIS: Two authors collected the data independently. We calculated the risk ratio (RR) or mean difference (MD) with 95% confidence intervals (CI) using the fixed-effect and the random-effects models based on available case-analysis. In the presence of only trials for a dichotomous outcome, we performed the Fisher's exact test. MAIN RESULTS: Overall, 17 trials with 736 patients met the inclusion criteria for this review. All trials had high risk of bias. Five hundred and one patients randomised in 11 trials provided information for various comparisons in this systematic review after excluding post-randomisation drop-outs and patients from trials that did not report any of the outcomes of interest for this review. The comparisons for which outcomes were available included pegylated (peg) interferon versus control; peg interferon plus ribavirin versus control; ribavirin plus peg interferon versus peg interferon; peg interferon (1.5 μg/kg/week) plus ribavirin versus peg interferon (0.5 μg/kg/week) plus ribavirin; amantadine plus peg interferon plus ribavirin versus peg interferon plus ribavirin; interferon versus control; interferon plus ribavirin versus control; ribavirin versus interferon; and ribavirin versus placebo. Long-term follow-up was not available in these trials. There were no significant differences in mortality, retransplantation, graft rejections requiring retransplantation or medical treatment, or fibrosis worsening between the groups in any of the comparisons in which these outcomes were reported. Quality of life and liver decompensation were not reported in any of the trials. There was a significantly higher proportion of participants who developed serious adverse events in the ribavirin plus peg interferon combination therapy group than in the peg interferon monotherapy group (1 trial; 56 participants; 17/28 (60.7%) in the intervention group versus 5/28 (17.9%) in the control group; RR 3.40; 95% CI 1.46 to 7.94). There was no significant difference in proportion of participants who developed serious adverse events or in the number of serious adverse events between the intervention and control groups in the other comparisons that reported serious adverse events. AUTHORS' CONCLUSIONS: Considering the lack of clinical benefit, there is currently no evidence to recommend or refute antiviral treatment for recurrent liver graft infection with hepatitis C virus. Further randomised clinical trials with low risk of bias and low risk of random errors with adequate duration of follow-up are necessary.

Diagnostic laboratories are under increasing pressure to improve and expand their services. Greater flexibility in sample processing is a critical factor that can improve the time to results while reducing reagent waste, making laboratories more efficient and cost-effective. The introduction of the Abbott mPLUS feature, with the capacity for extended use of amplification reagents, significantly increases the flexibility of the m2000 platform and enables laboratories to customize their workflows based on sample arrival patterns. The flexibility in sample batch size offered by mPLUS enables significant reductions in processing times. For hepatitis B virus tests, a reduction in sample turnaround times of up to 30% (105 min) was observed for batches of 12 samples compared with those for batches of 24 samples; for Chlamydia trachomatis/Neisseria gonorrhoeae tests, the ability to run batches of 24 samples reduced the turnaround time by 83% (54 min) compared with that for batches of 48 samples. Excellent correlations between mPLUS and m2000 standard condition results were observed for all RealTime viral load assays evaluated in this study, with correlation r values of 0.998 for all assays tested. For the qualitative RealTime C. trachomatis/N. gonorrhoeae assay, the overall agreements between the two conditions tested were >98% for C. trachomatis and 100% for N. gonorrhoeae. Comparable precision results were observed for the two conditions tested for all RealTime assays. The enhanced mPLUS capability provides clinical laboratories with increased efficiencies to meet increasingly stringent turnaround time requirements without increased costs associated with discarding partially used amplification reagents.


**BACKGROUND:** and Overview. Changes in the science of hepatitis C virus (HCV) infection and transmission in a private dental practice provide an opportunity to update dental health care providers about this pathogen. The authors’ aims in this review were to create awareness of health care- associated transmission of hepatitis C and provide an update on the changes in testing and treatment. The authors include data from population-based epidemiologic surveys, clinical practice guidelines, surveillance reports and practice protocols. **RESULTS:** In the United States, the elevated prevalence of chronic HCV infection among baby boomers—people born during the period from 1945 through 1965—led the Centers for Disease Control and Prevention to release new national screening guidelines. The authors summarize information about the natural history and epidemiology of hepatitis C and describe the new guidelines and novel treatment options. In addition, the authors provide an overview of how outbreaks of health care-associated HCV are detected and prevented. **Practical Implications.** Because dental health care professionals likely will treat people with current infection, education in the current science of HCV infection is useful.


Genome-wide association studies (GWAS) 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 (DAAs). 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 interferon-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 DAAs.


ABSTRACT BACKGROUND: Treatment uptake amongst patients with chronic Hepatitis C virus (HCV) in Australia is relatively low. New approaches to assessment have the potential to reduce public waiting lists, improve access to treatment, and to reduce healthcare costs. AIM: To describe the costs to the public hospital system and waiting time associated with a novel integrated rapid access to assessment and treatment (RAAT) model of care that utilizes Transient Elastography (TE) as a specialist outpatient-based approach for a streamlined assessment of patients with chronic HCV, compared to conventional outpatient management with liver biopsy (LB). METHODS: Time from first medical review to treatment plan and costs associated with detection of fibrosis were recorded for patients receiving RAAT during a 3-month period, and for a similar historical cohort managed conventionally with LB. Costs related to medical and multidisciplinary team reviews and the TE/LB test itself were included. Results: Patients receiving RAAT had lower costs (n = 27, median AU$2716) and shorter time to treatment (median = 194 days) than for conventional management (n = 13, median $5005, 420 days; p < 0.01). Differences related to the lower TE test costs and the lower cost of consults between first medical review and establishment of a treatment plan. CONCLUSIONS: Based on real world audit data, this evaluation suggests TE, used as part of a new RAAT model of care, is cost saving to the health system in the short-term and reduces waiting times. The analysis reported here was intended to assess the costs related to detection of fibrosis, and is limited by the small sample size and potential selection bias. Future research should undertake a full economic evaluation at a whole of service level, to consider a more comprehensive and longer-term assessment of the costs and benefits associated with HCV management.
Hepatitis C virus (HCV) infection affects about 160 million people worldwide. It is treated with pegylated-interferon (peg-IFN) and ribavirin, and in the case of patients affected by genotype 1, also with a protease inhibitor (telaprevir or boceprevir). Despite a good success rate, IFN-based combinations are contraindicated in several patients (e.g. decompensated cirrhosis, patients with psychiatric disorders, severe heart diseases or autoimmune disorders) and are associated with frequent adverse events that ultimately reduce their use. Numerous oral drugs are in an advanced phase of clinical development, and in some cases, in IFN-free combinations. This review focuses on preclinical and clinical data regarding daclatasvir (BMS-790052), which is a highly selective HCV NS5A replication complex inhibitor effective against HCV genotypes 1, 2, 3 and 4. In vitro data show that daclatasvir exerts a very potent antiviral effect against several HCV genotypes. Its pharmacokinetics is optimal and allows once-a-day oral administration. Its adverse event profile is good. Clinical data regarding its efficacy in combination with peg-IFN, ribavirin or other direct antiviral agents are impressive (rates of sustained virological response range between 60% and 100% in treatment-naive patients). The only drawback of this drug appears to be a relatively low genetic barrier to resistance. In conclusion, daclatasvir, especially in combinations with other antiviral agents, is a very promising drug for the treatment of chronic hepatitis C.

Children with HCV infection often differ from adults regarding the rate of viral clearance, duration of infection and progression to cirrhosis. In the pediatric population, vertical transmission of hepatitis C from mother to infant is the most common route of infection. In this review, we will explore the factors that may influence the natural history of HCV infection in children who acquire the infection through maternal-fetal transmission. There is particular focus on how viral diversity and the infant immune system may impact viral transmission. An enhanced understanding of maternal-fetal transmission of hepatitis C has the potential to impact effective drug and vaccine development for both children and adults.

Liver Cancer

Hepatocarcinogenesis in chronic hepatitis C patients achieving a sustained virological response to interferon: significance of lifelong periodic cancer screening for improving outcomes.
BACKGROUND: Due to advances in interferon (IFN) therapy for chronic hepatitis C, most elderly patients, and even many of those with advanced hepatic fibrosis, now achieve a sustained virological response (SVR). However, carcinogenesis remains problematic in these patients. Hence, we aimed to elucidate risk factors for hepatocarcinogenesis in SVR patients and to present an appropriate follow-up protocol for improving outcomes. METHODS: We
retrospectively studied 562 consecutive SVR patients for a median observation period of 4.8 years. **RESULTS:** Hepatocellular carcinoma was diagnosed in 31 patients (5.5%). Respective cumulative incidences were 3.1, 10.1, and 15.9% at 5, 10, and 15 years after completion of IFN therapy. The proportional hazards model identified moderate or advanced fibrosis stage, advanced age, habitual alcohol consumption, and alpha-fetoprotein elevation as determinants of carcinogenesis, with hazard ratios of 10.7 (p < 0.001), 4.1 (p < 0.01), 3.9 (p < 0.01), and 2.6 (p < 0.05), respectively. Carcinoma was diagnosed in 26% of patients more than 10 years after completion of IFN therapy. Unexpectedly, F2 fibrosis was detected in 42% of these patients. The 5-year survival rate was 93% in the patients who had received periodic cancer screening but only 60% in those who had not. **CONCLUSION:** We recommend that SVR patients be observed at 6-month intervals, at a minimum, to facilitate diagnosis at an early stage, for as long as possible after completion of therapy even if not at an advanced stage of fibrosis.


**OBJECTIVE:** To identify medical predictors of futility in recipients with laboratory Model of End-Stage Liver Disease (MELD) scores of 40 or more at the time of orthotopic liver transplantation (OLT). **BACKGROUND:** Although the survival benefit for transplant patients with the highest MELD scores is indisputable, the medical and economic effort to bring these highest acuity recipients through OLT presents a major challenge for every transplant center. **METHODS:** This study was undertaken to analyze outcomes in patients with MELD scores of 40 or more undergoing OLT during the period February 2002 to December 2010. The analysis was focused on futile outcome (3-month or in-hospital mortality) and long-term posttransplant outcome. Independent predictors of futility and failure-free survival were identified and a futility risk model was created. **RESULTS:** During the study period, 1522 adult cadaveric OLTs were performed, and 169 patients (13%) had a MELD score of 40 or more. The overall 1, 3, 5, and 8-year patient survivals were 72%, 64%, 60%, and 56%. Futile outcome occurred in 37 patients (22%). MELD score, pretransplant septic shock, cardiac risk, and comorbidities were independent predictors of futile outcome. Using all 4 factors, the futility risk model had a good discriminatory ability (c-statistic 0.75). Recipient age per year, life-threatening postoperative complications, hepatitis C, and metabolic syndrome were independent predictors for long-term survival in nonfutile patients (Harrels c-statistic 0.72). **CONCLUSIONS:** Short- and long-term outcomes of recipients with MELD scores of 40 or more are primarily determined by disease-specific factors. Cardiac risk, pretransplant septic shock, and comorbidities are the most important predictors and can be used for risk stratification in these highest acuity recipients.


**OBJECTIVES:** Historically, only 10% of patients with hepatocellular carcinoma (HCC) are
diagnosed with early-stage, potentially curable disease. In this study, chronic hepatitis virus-infected patients were prospectively screened to determine: (i) the proportion of patients diagnosed with potentially curable HCC, and (ii) survival following curative therapy.

**METHODS:** The study included 8900 chronic hepatitis virus-infected patients enrolled in a prospective screening programme, of whom 1335 (15.0%) were infected with hepatitis B virus (HBV), 7120 (80.0%) with hepatitis C virus (HCV), and 445 (5.0%) with both HBV and HCV. Screening was conducted every 6 months and included serum alpha-fetoprotein (AFP) measurement and ultrasonography. Curative treatments included liver transplantation, resection, radiofrequency ablation and/or ethanol injection. **RESULTS:** Hepatocellular carcinoma was diagnosed in 765 (8.6%) patients. Of 1602 patients with cirrhosis, 758 (47.3%) developed HCC. Curative treatment was possible in 523 (68.4%) of the 765 HCC patients. Two- and 5-year rates of overall survival in the curative treatment group were 65% and 28%, respectively, compared with 10% and 0% in the advanced disease group (P < 0.001). **CONCLUSIONS:** Prospective screening of patients at high risk for the development of HCC increases the proportion of patients diagnosed with potentially curable disease. This may result in an increase in the number of longterm survivors. Screening strategies should focus on patients with chronic HBV or HCV infection who have progressed to cirrhosis because more than 40% of these patients will develop HCC.


Nonalcoholic steatohepatitis (NASH) is currently the third leading indication for liver transplantation (LT) in the U.S. and is predicted to become the leading indication for LT in the near future. The trends in NASH-related hepatocellular carcinoma (HCC) among LT recipients in the U.S. remain undefined. We performed a retrospective cohort study to evaluate trends in the etiology of HCC among adult LT recipients in the U.S. from 2002 to 2012, utilizing national data from the United Network for Organ Sharing registry. From 2002-2012, there were 61,868 adults who underwent LT in the U.S., including 10,061 patients HCC. The total number and proportion of HCC LT recipients demonstrated a significant increase following the implementation of the model for end stage liver disease (MELD) scoring system in 2002 (3.3%, n=143 in 2000 vs. 12.2%, n=714 in 2005 vs. 23.3%, n=1336 in 2012). The proportion of HCV-related HCC increased steadily from 2002 to 2012, and HCV remained the leading etiology of HCC throughout the MELD era (43.4% in 2002 vs. 46.3% in 2007 vs. 49.9% in 2012). NASH-related HCC also increased significantly, and NASH is the second leading etiology of HCC-related LT (8.3% in 2002 vs. 10.3% in 2007 vs. 13.5% in 2012). From 2002 to 2012, the number of patients undergoing LT for HCC secondary to NASH increased by nearly 4-fold, and the number of LT patients with HCC secondary to HCV increased by 2-fold. **Conclusion:** NASH is the second leading etiology of HCC leading to LT in the U.S. More importantly, NASH is currently the most rapidly growing indication for LT in patients with HCC in the U.S. (Hepatology 2013;).

BACKGROUND: Hepatocellular carcinoma (HCC) is one of the most common human malignancies in the world, and its prognosis is generally poor. Epigenetic alteration such as DNA methylation has been shown to be important in the development of human cancers including HCC. Here, we analyzed the methylation status of ZAR1, which has been reported to be aberrantly methylated in a few human cancers.

METHODS: We investigated the methylation status of ZAR1 in 88 HCV-positive HCC and matched nontumorous liver tissue samples and 4 normal liver tissue samples used as a control using MassARRAY EpiTYPER. Further statistical analysis was performed to determine the relationship between methylation level and patient clinicopathological features and prognosis.

RESULTS: CpG islands in ZAR1 exon 1 showed a higher methylation level in all 88 HCC than in nontumorous tissues. The hypermethylation group, whose cancer tissues showed a twofold or higher methylation level compared with nontumorous tissues, showed a significantly higher serum AFP ($p = 0.018$) and lower serum albumin ($p = 0.001$) and single rather than multiple tumors ($p = 0.031$) compared with the hypomethylation group. Multivariate regression analyses were performed to identify which of the following factors were the predictors of the hypermethylation group: serum albumin, AFP, and tumor multiplicity. This study showed that patients who had Zar1 hypermethylation in the HCC tissues had a significantly lower serum albumin level than those in the hypomethylation group ($p = 0.007$).

CONCLUSION: Although it is still unknown how ZAR1 hypermethylation affects HCC development, it could be a potential marker to detect HCV-related HCC.