Clinical trials, cohort studies, pilot studies


Background AIMS: The impact of virological factors and interleukin-28B (IL-28B) genetic variants on retreatment of hepatitis C virus genotype 2 (HCV-2) treatment-experienced patients remains unknown. METHODS: On-treatment virological responses and IL-28B rs8099917 genotype were determined in 46 HCV-2 treatment-experienced patients (42 previous relapsers; four previous non-responders) retreated with 24-week peginterferon/ribavirin. RESULTS: Forty (87.0%) patients carried the rs8099917 TT genotype and 6 patients (13.0%) carried the TG/GG genotype. The sustained virological response (SVR; seronegativity of HCV RNA throughout 24 weeks of the post-treatment follow-up period) rate was 71.7%. Compared with previous non-responders, previous relapsers had a significantly higher SVR rate (78.6% vs. 0%, P=0.004) and a lower relapse rate (17.5% vs. 100%, P=0.04). All the previous non-responders were with the rs8099917 TT genotype. As for those who relapsed, treatment responses, including the rates of rapid virological response (RVR, 80.6% vs. 66.7%, P=0.59), early virological response (EVR, 97.2% vs. 83.3%, P=0.27), end-of-treatment virological response (97.2% vs. 83.3%, P=0.27) and SVR (80.6% vs. 66.7%, P=0.59) and relapse rate (17.1% vs. 20.0%, P=1) did not differ significantly between patients with the rs8099917 TT and those with the non-TT genotype. Multivariate analysis revealed that the most important factor predictive of an SVR in the retreatment of HCV-2 was previous relapse; the only factor predictive of an SVR for previous relapers was the achievement of an EVR. Compared with the achievement of a RVR, the attainment of an EVR was more accurate in predicting an SVR (88% vs. 74%).

Conclusions: Peginterferon/ribavirin is effective in the retreatment of HCV-2 relapers, especially among those who achieved an EVR.

BACKGROUND AND AIM: The most important factor influencing the effect of pegylated interferon (PEG-IFN)/ribavirin therapy (PEG) for chronic hepatitis C genotype 1b with high viral load is the interleukin 28B (IL28B) genotype. We investigated the usefulness of lead-in twice-daily interferon (IFN)-β/ribavirin therapy (IFN-β), and the early hepatitis C virus RNA (HCV-RNA) dynamics was compared between PEG and IFN-β groups according to the IL28B genotype. METHODS: Forty-six patients were randomly allocated to PEG and IFN-β groups, and HCV-RNA dynamics in an early phase of treatment were analyzed. RESULTS: The patients with minor IL28B genotype was 6/23 and 8/23 in IFN-β and PEG groups, respectively. In the patients with IL28B major genotype, viral load reduction was marginally greater in IFN-β group than in PEG group. In contrast, in the patients with the IL28B minor genotype, viral load reduction was significantly and numerically greater in IFN-β group than in PEG group at 1 week (2.07 vs 0.76 log IU/mL, P = 0.038), 2 weeks (2.73 vs 1.01, P = 0.009), 4 weeks (2.72 vs 1.55, P = 0.059), and 12 weeks (4.56 vs 3.24, P = 0.104). The sustained virological response rates in the IL28B major genotype were similar between IFN-β group (47.1%, 8/17) and PEG group (53.3%, 8/15). In contrast, the sustained virological response rates in the IL28B minor genotype were numerically higher in IFN-β group (50.0%, 3/6) than in PEG group (12.5%, 1/8), although not statistically significant. CONCLUSION: It was suggested that lead-in twice-daily IFN-β/ribavirin treatment followed by PEG-IFN/ribavirin combination therapy may modify the HCV-RNA dynamics compared with that by PEG-IFN/ribavirin therapy, and it is particularly useful for the IL28B minor genotype.


BACKGROUND: Interferon-alpha IFNa induced thyroid dysfunction (IITD) occurs in up to 20% of patients undergoing therapy for hepatitis C. The diversity of thyroid disease presentations suggests several different pathological mechanisms are involved, such as autoimmunity and direct toxicity. Elucidating the relationships between risk factors and disease phenotype provides insight into the mechanisms of disease pathophysiology. METHODS: We studied 869 euthyroid patients from the ACHIEVE 2/3 trial, a randomized international clinical trial comparing pegylated-IFNa2a weekly or albumin-IFNa2b every two weeks for up to 24 weeks in patients with hepatitis C, genotype 2 or 3, from 136 centers. The study population was 60% male and 55% white. Serum TSH and free T4 were measured before therapy, monthly during treatment from week 8, and at 4 and 12 week follow-up visits. RESULTS: Overall, 181 (20.8%) participants had at least one abnormal TSH during the study. Low TSH occurred in 71 (8.2%), of whom 30 (3.5%) had a suppressed TSH below 0.1 mU/L. Hypothyroidism occurred in 53 patients (6.1%), with peak TSH above 10 mU/L in 12 patients (1.4%). Fifty-seven patients had a biphasic thyroiditis (6.6%), with extreme values for the nadir and/or peak TSH in all but one. Medical therapy was given to one thyrotoxic patient, four hypothyroid patients and 26 biphasic
thyroiditis patients. Multivariate logistic regression analysis demonstrated that biphasic thyroiditis is associated with being female and higher pretreatment serum TSH, whereas being Asian or a current smoker decreased the risk of thyroiditis. Hypo- and hyperthyroidism are most strongly predicted by the pre-treatment TSH. CONCLUSIONS: Biphasic thyroiditis accounted for the majority (58%) of clinically relevant IITD. We confirmed our recent findings in a related cohort that female sex is a risk factor for thyroiditis but not hypothyroidism. Further, in this large multi-ethnic study, the risk of thyroiditis is dramatically increased, specifically for white women. Smoking was found to be protective of thyroiditis. These results support closer monitoring of women and those with a serum TSH at the extremes of the normal range during therapy so that prompt intervention can mitigate the consequences of thyroid dysfunction associated with IFNα treatment.


BACKGROUND: The uridine nucleotide analogue sofosbuvir is a selective inhibitor of hepatitis C virus (HCV) NS5B polymerase. We assessed the safety and efficacy of sofosbuvir in combination with pegylated interferon alfa-2a (peginterferon) and ribavirin in non-cirrhotic treatment-naive, patients with HCV. METHODS: For this open-label, randomised phase 2 trial, we recruited patients from 42 centres in the USA and Puerto Rico between March 23, 2011, and Sept 21, 2011. Patients were eligible for inclusion if they had chronic HCV infection (genotypes 1, 4, 5, or 6), were aged 18 years or older, and had not previously received treatment for HCV infection. Using a computer-generated randomisation sequence, we randomly assigned patients with HCV genotype-1 to one of three cohorts (A, B, and C; in a 1:2:3 ratio), with randomisation stratified by IL28B (CC vs non-CC allele) and HCV RNA (<800 000 IU/mL vs ≥800 000 IU/mL). Patients received sofosbuvir 400 mg plus peginterferon and ribavirin for 12 weeks (cohort A) or for 24 weeks (cohort B), or 12 weeks of sofosbuvir plus peginterferon and ribavirin followed by 12 weeks of either sofosbuvir monotherapy or sofosbuvir plus ribavirin (cohort C). We enrolled patients with all other eligible genotypes in cohort B. The primary efficacy endpoint was sustained virological response at post-treatment week 24 (SVR24) by intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, number NCT01329978. RESULTS: We enrolled 316 patients with HCV genotype-1: 52 to cohort A, 109 to cohort B, and 155 to cohort C. We assigned 11 patients with HCV genotype-4 and five patients with genotype-6 to cohort B (we detected no patients with genotype 5). In patients with HCV genotype-1, SVR24 was achieved by 46 patients (89%, 95% CI 77-96) in cohort A, 97 patients (89%, 82-94) in cohort B, and by 135 (87%, 81-92) in cohort C. We detected no difference in the proportion of patients achieving SVR24 in cohort A compared with cohort B (p=0.94), or in cohort C (p=0.78). Nine (82%) of 11 patients with genotype-4 and all five with genotype-6 achieved SVR24. Seven patients, all with genotype-1 infection, relapsed after completion of assigned treatment. The most common adverse events that led to the discontinuation of any study drug-anaemia and neutropenia-were associated with peginterferon and ribavirin treatment. Three (6%) patients in cohort A, 18 (14%) patients in cohort B, and three (2%) patients in cohort C discontinued treatment because of an adverse event. INTERPRETATION: Our findings suggest that sofosbuvir is well tolerated and that there is no additional benefit of extending
treatment beyond 12 weeks, but these findings will have to be substantiated in phase 3 trials. These results lend support to the further assessment of a 12 week sofosbuvir regimen in a broader population of patients with chronic HCV genotype-1 infection, including those with cirrhosis.


BACKGROUND: Protease inhibitors have improved treatment of infection with hepatitis C virus (HCV), but dosing, a low barrier to resistance, drug interactions, and side-effects restrict their use. We assessed the safety and efficacy of sofosbuvir, a uridine nucleotide analogue, in treatment-naive patients with genotype 1-3 HCV infection. METHODS: In this two-cohort, phase 2 trial, we recruited treatment-naive patients with HCV genotypes 1-3 from 22 centres in the USA. All patients were recruited between Aug 16, 2010, and Dec 13, 2010, and were eligible for inclusion if they were aged 18–70 years, had an HCV RNA concentration of 50 000 IU/mL or greater, and had no cirrhosis. We randomly allocated all eligible patients with HCV genotype 1 (cohort A) to receive sofosbuvir 200 mg, sofosbuvir 400 mg, or placebo (2:2:1) for 12 weeks in combination with peginterferon (180 μg per week) and ribavirin (1000–1200 mg daily), after which they continued peginterferon and ribavirin for an additional 12 weeks or 36 weeks (depending on viral response). Randomisation was done by use of a computer-generated randomisation sequence and patients and investigators were masked to treatment allocation until week 12. Patients with genotypes 2 or 3 (cohort B) received open-label sofosbuvir 400 mg plus peginterferon and ribavirin for 12 weeks. Our primary outcomes were safety and tolerability. Secondary efficacy analyses were by intention to treat and endpoints included sustained virological response, defined as undetectable HCV RNA at post-treatment weeks 12 and 24. This study is registered with ClinicalTrials.gov, number NCT01188772. FINDINGS: In cohort A, 122 patients were assigned 200 mg sofosbuvir (48 patients), 400 mg sofosbuvir (48), or placebo (26). We enrolled 25 patients into cohort B. The most common adverse events-fatigue, headache, nausea, and chills—were consistent with those associated with peginterferon and ribavirin. Eight patients discontinued treatment due to adverse events, two (4%) receiving sofosbuvir 200 mg, three (6%) receiving sofosbuvir 400 mg, and three (12%) receiving placebo. In cohort A, HCV RNA was undetectable at post-treatment week 12 in 43 (90%; 95% CI 77-97) of 48 patients in the 200 mg sofosbuvir group; 43 (91%; 80-98) of 47 patients in the 400 mg sofosbuvir group, and 15 (58%; 37-77) of 26 patients in the placebo group. In cohort B, 23 (92%) of 25 patients had undetectable HCV RNA at post-treatment week 12. INTERPRETATION: Our findings lend support to the further assessment, in phase 2 and 3 trials, of sofosbuvir 400 mg plus peginterferon and ribavirin for 12 weeks in treatment-naive patients with HCV genotype-1.

BACKGROUND & AIMS: There are limited data on the early effectiveness of direct-acting antiviral (DAA) therapies for patients with hepatitis C virus (HCV) infection in routine medical practice. We aimed to evaluate real-world experience with DAA-based regimens. METHODS: Using the Veterans Affairs' Clinical Case Registry, we conducted a prospective observational intent-to-treat analysis of veterans infected with HCV genotype 1 who began treatment with pegylated interferon, ribavirin, and boceprevir (BOC, n=661) or telaprevir (TVR, n=198) before January 2012. We determined rates of virologic response at treatment weeks 4, 8, 12, and 24; futility; early discontinuation; and adverse hematologic events. RESULTS: About one-third of patients discontinued treatment by week 24 (30% BOC, 34% TVR). A higher percentage of treatment-naïve, non-cirrhotic patients receiving BOC had undetectable levels of virus at week 24 than of patients receiving TVR (74% vs 60%; P =.03). There were no significant differences in rates of early response within subgroups of cirrhotics, prior relapsers, prior partial responders, or prior null responders. By week 24, treatment was determined to be futile for 14% of patients receiving BOC and 17% of those receiving TVR. No differences were observed in overall rates of anemia (50% BOC, 49% TVR) or thrombocytopenia (16% BOC, 18% TVR); higher rates of neutropenia were observed in BOC-treated patients (34% BOC, 21% TVR; P =.008). CONCLUSION: HCV-infected Veterans treated in routine medical practice with DAA-based regimens (BOC or TVR) had rates of early response comparable to those reported in clinical trials. However, they had higher rates of futility and early discontinuation than clinical trial participants. Further studies are needed to determine rates of sustained viral response.


AIM: Optimal management of hepatitis C virus (HCV) infection is controversial in heavy drinkers. We compared the management of HCV infection of heavy drinkers with that of patients without a history of alcohol abuse. METHODS: In a retrospective case-control study, 69 HCV-infected heavy drinkers [daily alcohol consumption at referral above 60 g/day, hereafter 'alcohol group'] were compared with matched HCV-infected patients with low alcohol consumption (<40 g/day, 'control group'). RESULTS: Patients of the 'alcohol group' were younger (42 vs. 45 years, P = 0.05), more often male (69.6 vs. 56.5%, P = 0.11) and had been infected by intravenous drug use (85.5 vs. 45.0%, P < 0.0001). The percentage of patients with a recommendation for treatment according to the French 2002 consensus (bridging fibrosis or genotype 2 or 3) was 52 of 69 (75.4%) in both groups, while the proportion of patients treated was higher in the control group (71.0 vs. 44.9%, P = 0.002). In the 'alcohol group', patients had better access to treatment if they were employed or consumed 170 g/day or less at first referral. Sustained virological response (SVR) was obtained in 10 of 31 patients (32.3%) of the 'alcohol group' vs. 8 of 31 patients (25.8%) of the control group matched for genotype and type of treatment (P = 0.58). CONCLUSION: Heavy drinkers are less often considered for antiviral therapy compared with patients without a history of alcohol abuse. However, once treatment is actually initiated, SVR rates are comparable with those achieved in non-drinkers despite the continuation of alcohol consumption during therapy in some patients.
In a sentinel cohort, hepatitis C virus (HCV) patients (primarily genotype [GT] 1a) were treated with daclatasvir (NS5A inhibitor) and asunaprevir (NS3 protease inhibitor). Pre-existence, emergence, and persistence of resistance variants in patients who failed this treatment are described. HCV-infected null-responders received daclatasvir (60 mg once daily) and asunaprevir (600 mg twice daily) alone (Group A, 11 patients) or with peginterferon alfa-2a and ribavirin (Group B, 10 patients) for 24 weeks. Resistance testing was performed on baseline samples and samples with HCV RNA =1000 IU/mL at Week 1 through post-treatment Week 48. Resistance substitution susceptibility to inhibition by asunaprevir and daclatasvir was assessed using HCV replicon assays. In Group A, 6 GT1a patients experiencing viral breakthrough and 1 GT1a patient who relapsed had detectable NS5A (Q30E/R, L31V/M, Y93C/N) and NS3 (R155K, D168A/E/V/Y) resistance-associated variants at failure. Two of 6 viral breakthrough patients achieved SVR48 after treatment intensification with peginterferon alfa-2a and ribavirin. For 2/4 viral breakthrough patients not responding to treatment intensification, NS3 resistance variants changed (D168Y to D168T; R155K to V36M-R155K). At post-treatment week 48, daclatasvir-resistant variants persisted while asunaprevir-resistant variants were generally replaced by wild-type sequences. The NS3 sequence remained unchanged in the one patient with NS3-R155K at baseline, relapse and post-treatment week 48. In Group B, no viral breakthrough was observed. **CONCLUSIONS:** Treatment failure of daclatasvir and asunaprevir in HCV GT1a patients was associated with both NS5A and NS3 resistance variants in prior null-responders. NS5A resistance variants persisted while NS3 resistance variants generally decayed suggesting a higher relative fitness of NS5A variants.

Progesterone suppresses interferon signaling by repressing TLR-7 and MxA expression in peripheral blood mononuclear cells of patients infected with hepatitis C virus.
This study aimed at investigating the effect of progesterone on interferon signaling pathways in peripheral blood mononuclear cells (PBMCs) of patients infected with hepatitis C virus (HCV). PBMCs were isolated from peripheral blood of 38 treatment-naïve HCV-infected patients, pooled, and stimulated with progesterone in the presence and absence of its receptor antagonist, mifepristone, along with interferon alpha (IFN-α) or imiquimod. Toll-like receptor (TLR) 7 and myxovirus resistance protein A (MxA) were quantified in PBMCs using RT-qPCR. Imiquimod alone or combined with progesterone did not change MxA expression in HCV-infected PBMCs. Progesterone decreased the inducing effect of IFN-α on TLR-7 expression in both males and females. Moreover, progesterone stimulation prior to IFN-α treatment attenuated the Jak/STAT pathway, which was reflected by decreased expression of MxA in females. Progesterone showed a negative impact on the IFN signaling pathway in HCV-infected PBMCs as it decreased the expression of TLR-7 in both genders, while MxA expression was decreased only in females.

BACKGROUND & AIMS: A substantial proportion of patients with chronic hepatitis C virus infection treated with pegylated interferon α/ribavirin fails to achieve sustained virological response (SVR). Since growing evidence suggests that innate immunity may influence treatment responses, we examined natural killer (NK) cell phenotypic and functional changes during standard antiviral therapy. METHODS: Expression of several NK cell regulatory molecules was evaluated by flow cytometry in 37 consecutive patients with chronic HCV infection at baseline and at different time points during and after discontinuation of treatment. Cytokine production was evaluated by intracellular staining. Cytolytic potential was assessed as degranulation and as antibody-dependent cytotoxicity. RESULTS: Baseline frequencies of CD56dim NK cells and perforin content were significantly higher, whereas CD16 expression was lower, in SVR vs. non-responder subjects. Analysis by linear regression for repeated measures during the first 12 weeks showed significantly increased frequencies of activated (CD69+) NK cells in rapid virological responders (RVR) and identified a typical NK cell profile associated with SVR, featuring higher NK perforin content, lower CD16 expression, and higher proportion of CD56dim/CD16- cells. Moreover, SVR patients displayed higher natural and antibody-dependent NK cytolytic potential. IL28B rs12979860 CC homozygosis was significantly associated with SVR, independently of NK cell phenotype and function. CONCLUSIONS: Different NK cell phenotypic and functional features in patients with chronic hepatitis C treated with standard therapy were observed between non-responder versus SVR patients, suggesting a potential role of NK cells in the response to treatment.


BACKGROUND: Chronic hepatitis C virus (HCV) infection is frequently associated with extrahepatic autoimmune disorders while interferon (IFN) and ribavirin treatment may exacerbate these conditions. Autoantibodies from HCV patients identify a novel indirect immunofluorescence (IIF) pattern on HEp-2 cells characterized by cytoplasmic rods and rings (RR). Our objectives were to determine the prevalence and clinical associations of RR autoantibodies in HCV patients, and identify related novel autoantibody targets. METHODS: Sera from 315 patients with HCV (301 treatment naive, 14 treated with interferon and/or ribavirin) were analyzed for the presence of RR antibodies by IIF on commercially available HEp-2 cell substrates. Antibodies to inosine monophosphate dehydrogenase 2 (IMPDH2) and cytidine triphosphate synthase 1 (CTPS1) were detected by addressable laser bead assay and other potential targets were identified by immuno-screening a protein microarray. Clinical and demographic data including HCV genotype, mode of infection, prior antiviral therapy, and histological findings were compared between RR antibody positive (RR+) and negative (RR-) patients. RESULTS: The median age of the HCV cohort was 51 years, 61% were male, and 76% were infected with HCV genotype 1 (G1). Four percent (n=14) had been treated with IFN-based therapy (IFN monotherapy, n=3; IFN/ribavirin, n=11); all had a sustained virologic response. In total, 15 patients (5% of the cohort) were RR+. RR+ and RR- patients had similar demographic
and clinical characteristics including age, sex, mode of HCV infection, prevalence of the G1 HCV genotype, and moderate to severe fibrosis. Nevertheless, RR+ patients were significantly more likely than RR- cases to have been treated with IFN-based therapy (33% vs. 3%; adjusted odds ratio 20.5 [95% confidence interval 5.1-83.2]; P<0.0005). Only 1/10 RR positive sera had detectable antibodies to IMPHD2 and none had antibodies to CTPS1. Potentially important autoantibody targets identified on protein arrays included Myc-associated zinc finger protein (MAZI) and ankyrin repeat motif. CONCLUSION: The majority of HCV patients with RR autoantibodies previously received IFN/ribavirin antiviral therapy. Further studies are necessary to determine the genesis of intracellular RR and elucidate the clinically relevant autoantigens as well as the clinical and prognostic significance of their cognate autoantibodies.


BACKGROUND: Steatosis and insulin resistance induced by hepatitis C virus (HCV) infection are, at least in part, critical factors for the progression of chronic hepatitis C (CHC) and can influence the outcome of antiviral treatment. Silent information regulator 1 (SIRT1) and adenosine monophosphate-activated protein kinase (AMPK) play a key role in the regulation of hepatic glucose and lipid metabolism. The aim of this study was to investigate the possible effect of HCV core protein on energy, glucose, and lipid metabolism of hepatocytes and expression of SIRT1 and AMPK. METHODS: HCV core protein expression plasmid was transfected into HepG2 cells. The level of reactive oxygen species (ROS) and values of NAD+/NADH and ATP/ADP were detected. Intracellular levels of triacylglycerol (TG), cholesterol, glucose uptake by hepatocytes, and glucose production were measured. The expression levels of mRNA and protein of SIRT1 and AMPK were detected. The mRNA levels of SIRT1 and AMPK downstream glucose and lipid metabolism genes were measured. RESULTS: In HepG2 cells expressing HCV core protein, the level of ROS increased, the value of NAD+/NADH decreased, the activity and expression levels of mRNA and protein of SIRT1 and AMPK decreased, glucose uptake and its regulator gene GLUT2 mRNA levels decreased, glucose production and its regulator genes PEPCK and G6Pase mRNA levels increased, intracellular TG and cholesterol contents and their regulator gene (SREBP-1c, FAS, ACC, HMGR, and HMGS) mRNA levels increased, the glycolytic gene GK and fatty acid oxidation genes PPARα and CPT1A mRNA levels decreased. CONCLUSIONS: HCV core protein induces alterations in cellular redox state (decrease in the NAD+/NADH ratio), which could influence the activity of SIRT1 and secondarily AMPK, then change the expression profile of glucose and lipid metabolism-related genes, thereby causing metabolism disorders of hepatocytes.

HIV/HCV COINFECTION

Acute hepatitis C infection in the context of HIV is an emerging problem in men who have sex with men (MSM). We conducted a retrospective cohort study of MSM diagnosed with and treated for acute hepatitis C infection over 10 years. Genotype 1 was the commonest type representing 69% of cases; the spontaneous clearance rate was 20%. The overall sustained virological response (SVR) rate on an intention-to-treat basis was 83%; SVR and was 92% for those completing 48 weeks of treatment. The presence of detectable RNA at week 12 had a 100% negative predictive value for SVR. This is the largest single cohort treated with 48 weeks of interferon and ribavirin and the treatment SVR is one of the highest reported. We propose that a 48-week treatment regimen may be superior to shorter (24-week) regimens though we acknowledge the need for a randomized controlled trial.

Current management of hepatitis C virus infection in patients with HIV co-infection.
As a result of shared routes of transmission, coinfection with hepatitis C virus (HCV) is common in human immunodeficiency virus (HIV)-infected patients. The prevalence of HIV/HCV coinfection is particularly high among persons who have used injection drugs; however, more recently, sexual transmission of HCV has been recognized among HIV-infected men who have sex with men (MSM). Over the past decade, the effectiveness of HIV treatment improved substantially, leading to a substantial reduction in HIV/AIDS-related deaths; in this context, liver disease due to HCV infection has emerged as major concern for co-infected patients. Over the same period, treatment of HCV remained stagnant, with pegylated interferon alfa (PegIFN) plus ribavirin (RBV; PegIFN/RBV) entrenched as the standard treatment for HCV infection for co-infected patients, who have the greatest risk for liver disease. However, the effectiveness of HCV treatment in this population has been disappointing because of low rates of treatment initiation and success. In 2011, novel HCV NS3/4A PIs (PIs), telaprevir and boceprevir, were approved for use in combination with PegIFN/RBV for the treatment of HCV genotype 1 infection; at the time of approval, important questions regarding the efficacy, safety, and potential for drug interactions with telaprevir and boceprevir had not been answered. More recently, data from drug-interaction studies and 2 small, phase II clinical trials indicate that these HCV treatment regimens may lead to higher rates of HCV eradication in HIV/HCV-coinfected patients, with manageable toxicity and pharmacologic interactions with antiretroviral drugs. As such, these HCV PI-based regimens have emerged as the standard for the treatment of HCV genotype 1 infection in carefully selected HIV-infected patients.

Plasma proteome analysis reveals overlapping, yet distinct mechanisms of immune activation in chronic HCV and HIV infections.
BACKGROUND: Human immunodeficiency virus (HIV) infection contributes to accelerated rates of progression of liver fibrosis during hepatitis C virus (HCV) infection, and HCV liver disease contributes to mortality during HIV infection. Although mechanisms underlying these interactions are not well known, soluble and cellular markers of immune activation associate with disease progression during both infections. METHODS: We identified proteins varying in expression across the plasma proteomes of subjects with untreated HIV infection, untreated HCV infection with low AST/platelet ratio-index (APRI), untreated HCV infection with high APRI,
HIV-HCV co-infection, and controls. We examined correlations between dysregulated proteins and markers of immune activation to uncover biomarkers specific to disease states. **RESULTS:** We observed the anticipated higher frequencies of HLADR+CD38+CD4 and CD8 T-cells, higher serum sCD14 levels, and higher serum IL-6 levels for HCV and HIV infected groups compared to controls. Plasma proteome analysis identified 2,297 peptides mapping to 227 proteins, and quantitative analysis of peptide intensity identified significant changes in 85 proteins across the five groups. Abundance for seven of these proteins was validated by ELISA. Forty-three of these proteins correlated with markers of immune activation, including at least two proteins that may directly drive T-cell activation. As a functional validation, we tested the enzymatic pathway product (lysophosphatidic acid, LPA) of one such protein, ENPP2, for ability to activate T-cells in vitro. LPA activated T-cells to express CD38 and HLA-DR.

**CONCLUSIONS:** These data indicate elevated levels of ENPP2 and LPA during advanced HCV disease may play a role in exacerbating immune activation during HCV-HIV co-infection.


**BACKGROUND:** The objective of this study was to determine the impact of sustained virologic response (SVR) to pegylated interferon (peg-IFN) plus ribavirin (RBV) on the incidence of liver-related complications and overall mortality in human immunodeficiency virus (HIV)-infected patients with compensated hepatitis C virus (HCV)-related cirrhosis. **METHODS:** We included in this prospective cohort study 166 coinfectected patients with compensated cirrhosis, who received peg-IFN plus RBV, to assess the time from the starting date of HCV therapy to the first hepatic decompensation and death due to any cause. **RESULTS:** SVR was observed in 43 (25%) individuals. Two (4.6%) patients with SVR developed liver decompensation vs 33 (26.8%) individuals without SVR (P = .002). The incidence of liver-related complications was 0.89 cases per 100 person-years (95% confidence interval [CI], .11-3.1) in SVR patients and 6.4 cases per 100 person-years (95% CI, 4.5-8.9) in non-SVR patients. Factors independently associated with liver decompensation were non-SVR (hazard ratio [HR], 8.1; 95% CI, 1.08-61.5; P = .042) and MELD score ≥9 at baseline (HR, 2.9; 95% CI, 1.2-7.2; P = .016). Two (4.6%) patients with SVR died due to any cause compared with 22 (17.9%) individuals without SVR (P = .02). MELD score ≥9 (HR, 3.1; 95% CI, 1.3-7.7; P = .011) and non-SVR (HR, 8.0; 95% CI, 1.07-61; P = .043) were independently associated with overall mortality. **CONCLUSIONS:** The achievement of SVR following peg-IFN plus RBV markedly reduces the incidence of liver-related decompensation and the overall mortality in HIV/HCV-coinfected patients with compensated cirrhosis.


**OBJECTIVES:** Many HIV-infected patients with chronic hepatitis C virus (HCV) infection do not receive treatment for HCV infection, often because of contraindications or poor adherence to anti-HIV therapy. The aim of this study was to identify factors influencing guideline-based HCV treatment initiation.
treatment initiation in a large cohort of HIV/HCV-coinfected patients. **METHODS:** Between 2005 and 2011, 194 (40.5%) of 479 coinfected patients not previously treated for HCV infection started this treatment based on current recommendations, i.e. a Metavir score > F1 for liver fibrosis; HCV genotype 2 or 3 infection; or HCV genotype 1 or 4 infection and low HCV viral load (< 800 000 IU/mL), whatever the fibrosis score. Clinical and biological data were compared between patients who started HCV therapy during follow-up and those who did not. **RESULTS:** In multivariate analyses, good adherence to treatment for HIV infection, as judged by the patient's physician, was associated with HCV treatment initiation [odds ratio (OR) 2.37; 95% confidence interval (CI) 1.17-4.81; P = 0.017], whereas patients with children (OR 0.53; 95% CI 0.30-0.91; P = 0.022) and those with cardiovascular disease or respiratory distress (OR 0.10; 95% CI 0.01-0.78; P = 0.03) were less likely to be treated. **CONCLUSIONS:** Adherence to treatment for HIV infection, as judged by the patient's physician, appears to have a major influence on the decision to begin treatment for HCV infection in coinfected patients. This calls for specific therapeutic education and adherence support in order to ensure timely anti-HCV therapy in this population.


**BACKGROUND:** Hepatitis C is a leading cause of mortality among HIV-infected individuals. Therefore, eradication of HCV in this population is a priority. There are scarce data regarding retreatment efficacy of HIV/HCV coinfected patients. The aim of our study was to evaluate efficacy, predictors of response, and long term clinical benefits of sustained virological response (SVR) after hepatitis C retreatment in a population of HIV/HCV coinfected patients. **MATERIAL AND METHODS:** We evaluated efficacy, safety, and clinical benefits of peginterferon(alfa-2a or alfa-2b) and ribavirin in a restrospective, observational, multicentric study, including 47 HIV/HCV coinfected patients, non-responders to previous treatment with conventional interferon alfa-2a and ribavirin. The primary endpoint of efficacy was SVR, defined as undetectable viral load 24 weeks after end of treatment. Death, liver disease progression, CD4 counts, and AIDS defining illness were the endpoints to access clinical benefits of treatment response. **RESULTS:** In our analysis, 31.9% patients reached SVR. Genotypes 2/3 had a significant better SVR (66.7%) compared to genotypes 1/4 (33.3%) (p = 0.022). During follow-up, deaths (6.89%) and hepatic decompensation (28.6%) occurred only in the nonresponder group, while there were no cases of death or hepatic decompensation among the responder group (p = 0.037). **CONCLUSION:** Nearly one third of patients (mainly those with genotypes 2/3) reached SVR after hepatitis C retreatment in this group of HIV/HCV coinfected patients. SVR was protective against hepatic decompensation and death in a two-year follow-up period. Retreatment may be an effective and safe way to eradicate HCV until new anti-HCV drugs become available to this group of patients.
The consumption of green tea (Camellia sinensis) has been shown to have many physiological and pharmacological health benefits. In the past two decades several studies have reported that epigallocatechin-3-gallate (EGCG), the main constituent of green tea, has anti-infective properties. Antiviral activities of EGCG with different modes of action have been demonstrated on diverse families of viruses, such as Retroviridae, Orthomyxoviridae and Flaviviridae and include important human pathogens like human immunodeficiency virus, influenza A virus and the hepatitis C virus. Furthermore, the molecule interferes with the replication cycle of DNA viruses like hepatitis B virus, herpes simplex virus and adenovirus. Most of these studies demonstrated antiviral properties within physiological concentrations of EGCG in vitro. Nevertheless, the antibacterial effects of EGCG alone and in combination with different antibiotics have been intensively analysed against a number of bacteria including multidrug-resistant strains such as methicillin-resistant Staphylococcus aureus or Stenotrophomonas maltophilia. Furthermore, the catechin EGCG has antifungal activity against human-pathogenic yeasts like Candida albicans. Although the mechanistic effects of EGCG are not fully understood, there are results indicating that EGCG binds to lipid membranes and affects the folic acid metabolism of bacteria and fungi by inhibiting the cytoplasmic enzyme dihydrofolate reductase. This review summarizes the current knowledge and future perspectives on the antibacterial, antifungal and antiviral effects of the green tea constituent EGCG.

Epidemiology, Diagnostics, and Miscellaneous Works


BACKGROUND AND AIM: There is sparse epidemiologic data on co-infection of hepatitis B (HBV) and hepatitis C (HCV) in the United States. Therefore, the aim of this study was to determine the prevalence and predictors of HBV co-infection in a large United States population of HCV patients. METHODS: We used the National Veterans Affairs HCV Clinical Case Registry to identify patients tested for HCV during 1997-2005. Patients were categorized based on HCV exposure (any +HCV tests or one test with a diagnostic code), HCV infection (+RNA or genotype), HBV exposure (any +HBV test, excluding +HBsAb only) and HBV infection (+HBsAg, HBV DNA, or HBeAg). The prevalence of HBV exposure among patients with HCV exposure and that of HBV infection among patients with HCV infection were determined. Multivariable logistic regression evaluated potential demographic and clinical predictors of HBV co-infection. RESULTS: Among 168,239 patients with HCV exposure, 58,415 patients had HBV exposure for a prevalence of 34.7% (95% CI 34.5-35.0). Among 102,971 patients with HCV infection, 1,431 patients had HBV co-infection for a prevalence of 1.4% (95% CI 1.3-1.5). Independent associations with HBV co-infection compared with HCV.
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mono-infection were age ≤ 50 years, male sex, positive HIV status, history of hemophilia, sickle cell anemia or thalassemia, history of blood transfusion, cocaine and other drug use; there was decreased risk in patients of Hispanic ethnicity. CONCLUSIONS: This is the largest cohort study in the United States on the prevalence of HBV co-infection in HCV patients. Among veterans with HCV, exposure to HBV is common (~35%), but HBV co-infection is relatively low (1.4%). Several possible risk factors were identified.


BACKGROUND & AIM: Transient elastography (TE) is a validated non-invasive tool to evaluate hepatic fibrosis in patients with hepatitis C virus (HCV) infection. Whether TE may sense changes of liver fibrosis following therapeutic HCV eradication has never been evaluated.

MATERIALS AND METHODS: 38 HCV cirrhotics with paired pre- and post-sustained virological response (SVR) liver biopsies (LB) underwent TE at the time of post-SVR LB. Liver fibrosis was staged with the META VIR scoring system and the area of fibrosis (%) was assessed morphometrically. RESULTS: Thirty-three patients had valid TE measurements after 61 (48-104) months from an SVR, and 20 (61%) of them had cirrhosis regression. On post-SVR LB, the median area of fibrosis was 2.3%, being significantly reduced from baseline (p<0.0001). Median TE value was 9.8 kPa being lower in regressed vs not regressed patients (9.1 kPa vs 12.9 kPa, p=0.01). TE was <12 kPa in 5 (38%) F4 patients and in 19 (95%) ≤ F3 patients (p=0.0007). The diagnostic accuracy of TE for diagnosing F4 after treatment was 58% sensitivity, 90% specificity, 6.1 LR +, 0.4 LR-, AUROC 0.77. A significant correlation was found between TE and both fibrosis stage (r=0.56; p=0.001) and morphometry (r=0.56, p=0.001) as well as between fibrosis stage and area of fibrosis (r=0.72, p=0.0001). CONCLUSIONS: Following therapeutic eradication of HCV, the predictive power of the viremic cut-off of 12 kPa was low as a consequence of liver remodelling and fibrosis reabsorption. LB still remains the only reliable approach to stage liver fibrosis following an SVR.


BACKGROUND AND GOALS: There are limited data on the extent to which medical providers adhere to practice guidelines for the antiviral treatment of patients with chronic hepatitis C virus (HCV) infection. As representative of overall provider adherence to practice guidelines, provider adherence to specific recommendations regarding rapid virologic response (RVR) was assessed. STUDY: From the Department of Veterans Affairs' Clinical Case Registry, all patients with HCV genotype 1 who initiated peginterferon and ribavirin between January 1, 2007 and December 31, 2008 were identified. The rate of testing for RVR was determined. Patient, provider, and facility characteristics were assessed to determine the factors that predicted improved provider adherence. For patients who achieved RVR, the overall treatment duration was calculated as a secondary measure of provider adherence. RESULTS: About one half of the cohort (54%) had HCV RNA testing for RVR. Among several significant predictors, testing for
RVR was more likely in gastroenterology/hepatology specialty clinics, by midlevel providers such as nurse practitioners and physician assistants, and in facilities with a higher volume of HCV patients. Most patients who achieved RVR completed a treatment course within the recommended range. However, 27% of the cohort received more or less than the recommended duration of treatment, thereby unnecessarily increasing their risk for adverse events or decreasing their potential for cure. CONCLUSIONS: More aggressive education is needed to improve provider adherence to HCV antiviral treatment guidelines and optimize the outcomes of HCV patients, especially with the recent approval of complicated direct-acting antiviral regimens.


BACKGROUND: Hepatitis C virus (HCV) is the most common chronic blood-borne infection in the United States and will become an increasing source of morbidity and mortality with aging of the infected population. Our objective was to develop decision analytic models to explore the cost-effectiveness of screening in populations with varying prevalence of HCV and risks for fibrosis progression. METHODS: We developed a Markov state transition model to examine screening of an asymptomatic community-based population in the United States. The base case was an ethnically and gender-mixed adult population with no prior knowledge of HCV status. Interventions were screening followed by guideline-based treatment, or no screening. Effectiveness was measured in quality-adjusted life-years (QALYs), and costs were measured in 2011 US dollars. RESULTS: In the base case (US population, 49% male, 78% white, 13% African American, and 9% Hispanic, mean age, 46 years), screening followed by guideline-based treatment (using boceprevir as the direct-acting antiviral agent) of those with chronic HCV infection costs $47 276 per QALY. The overall HCV prevalence in the United States is reported to be 1.3%-1.9%, but prevalence varies markedly among patients with different numbers and types of risk factors. The marginal cost-effectiveness ratio (mCER) of screening decreases as prevalence increases. Below a prevalence of 0.84%, the mCER is greater than the generally accepted societal willingness-to-pay threshold of $50 000 per QALY and thus is not considered highly cost-effective. CONCLUSIONS: Targeted screening is cost-effective when prevalence of HCV exceeds 0.84%. Prospective evaluation of a screening tool is warranted and should include comparisons with other screening strategies.


INTRODUCTION: Accurate genotyping of hepatitis C virus (HCV) is important in determining the optimal regimen, dose and duration of antiviral therapy of chronic HCV, as well as estimating the response rate. The 5-untranslated region (5’UTR) of HCV RNA is used in commercial genotyping, but probes and lengths of amplicons are proprietary and vary across assays. OBJECTIVE: Evaluation of the HCV 5’UTR for factors involved in reliable determination of HCV genotypes. STUDY DESIGN: Serum from four subjects with chronic HCV with disparate results on commercial genotyping and four controls were analyzed. HCV RNA was extracted from serum samples and the 5’UTR and NS5B region were sequenced. Ten
clones from each region were compared to prototype sequences and analyzed for genotype assignment using five programs. Results were compared to commercial assays. 5'UTR sequences were sequentially shortened from either the 5' end or 3' end, or both, with genotyping of resultant fragments. **RESULTS:** Sequences were obtained for the 5'UTR in all eight subjects, but for the NS5B in five. Genotype assignment was identical between the two regions in those 5 with complete sequencing. Genotyping by sequencing gave different results from the commercial assays in the four experimental samples but agreed in the four controls. Shortening of sequences affected results and sequences of less than 200 bases were inaccurate. Neither Hamming distance nor quasispecies affected results. **CONCLUSION:** Sequencing of the HCV 5'UTR provided reliable genotyping results and resolved discrepancies identified in commercial assays, but genotyping by sequencing was highly dependent upon sequence length.


**BACKGROUND:** Although it has been reported that hepatitis C virus (HCV) infection is associated with a significant decline in health-related quality of life (HRQOL), the underlying causes and mechanisms are still unknown. Insulin resistance (IR) is recognized as a distinct aspect of chronic HCV infection. Therefore, we attempted to identify the factors including IR indices that are related to the HRQOL of patients with chronic hepatitis C (CHC). **METHODS:** One hundred and seventy-five CHC patients (91 female, 84 male, mean age, 56.4 years) not using antidiabetic agents were included and underwent a 75-g oral glucose tolerance test (OGTT) and completed a self-administered HRQOL questionnaire, the Short Form 36 (SF-36), which is a well-validated questionnaire for assessing general QOL. Scale scores were standardized and summarized into physical and mental component summary (PCS and MCS). We investigated which clinical parameters, including homeostasis model assessment of insulin resistance (HOMA-IR), were associated with decline in PCS and MCS scores in CHC patients.  
**RESULTS:** There were no significant differences in clinical parameters between high and low MCS, but there were significant differences in age, sex, hemoglobin, liver fibrosis, OGTT pattern, and HOMA-IR between high and low PCS. Multivariate analysis showed that HOMA-IR >2 was independently associated with lower PCS (OR 2.92, p < 0.01). **CONCLUSIONS:** Our results suggest that impairment of HRQOL, especially physical domains, in CHC patients is associated with IR.

**Birth Cohort Screening for Chronic Hepatitis During Colonoscopy Appointments.** Sears DM, Cohen DC, Ackerman K, Ma JE, Song J. Am J Gastroenterol. 2013 Mar 19. doi: 10.1038/ajg.2013.50. [Epub ahead of print]  

**OBJECTIVES:** More than 70% of infections with hepatitis C viruses (HCV) occur among people born between 1945 and 1965 (baby boomers). The US Centers for Disease Control estimate that 70% of people with chronic hepatitis are not aware that they are infected with a virus. We performed a prospective trial to determine whether people born during this time period would accept testing for chronic viral infection (hepatitis B virus (HBV) and HCV) during routine colonoscopies. We also evaluated acceptance and efficacy of screening for immunity to hepatitis A (HAV) and B viruses. **METHODS:** During a 3-month period, 500 people, 50-65
years old, who received a colonoscopy were offered a test for viral hepatitis. Patients answered questions about vaccination, exposure, diagnoses, and risk factors related to viral hepatitis, and blood samples were collected. Patients who tested positive for antibodies to HCV or hepatitis B surface antigen (HBsAg) were contacted for further testing and possible therapy. Patients without immunity to HAV or HBV were offered vaccinations. **RESULTS:** Three hundred and seventy-six people (158 men) agreed to be tested. Four were found to have antibodies against HCV and one had detectable virus. None of the patients tested positive for HBsAg; 136 (36%) had at least one risk factor for chronic hepatitis and 31 (8%) had multiple risk factors. Three hundred and fifteen patients (84%) were not immune to HAV, HBV, or both viruses. **CONCLUSIONS:** It is possible to screen patients for viral hepatitis during visits for routine colonoscopy. This approach can identify individuals with undiagnosed chronic HBV and HCV infections who could benefit from education, vaccination, or therapy.


**BACKGROUND:** The diagnosis of autoimmune hepatitis (AIH) is already difficult, and that of AIH with chronic viral hepatitis including hepatitis B (HBV) or hepatitis C (HCV) is even more challenging. To date, only a few case-based studies have described this association. **AIM:** The aim was to retrospectively assess diagnostic difficulties, therapeutic approaches, and performance of the scoring systems in AIH patients with concurrent HBV and HCV. **METHODS:** A total of 25 patients from United States, Sweden, Italy, and Turkey were retrospectively evaluated. Both revised and simplified criteria suggested by the International Autoimmune Hepatitis Group were applied for each patient. All study data were obtained from medical records. Results. Of the 25 patients, 20 (80%) had concomitant HCV and 5 (20%) had HBV. Based on the revised scoring system and simplified criteria, 18 (72%) and 12 (48%) patients were diagnosed as "probable" AIH. None of the patients were diagnosed as "definite" AIH according to both scoring systems. Patients with HCV initially were treated with immune-suppressive agents, and antiviral therapy was commenced when biochemical remission occurred. AIH patients with HBV were first treated with antiviral and thereafter, immune-suppressive therapy was started. **CONCLUSIONS:** This large case series describes concurrent AIH and chronic viral hepatitis. The revised scoring system for AIH had a better performance than the simplified scoring system. However, neither scoring system is optimal for diagnosing AIH alone. In these patients, a definitive diagnosis of AIH should be based on a combination of serological profiles, histological findings, scoring systems, treatment response, and outcomes.


The standard of care therapy of chronic hepatitis C with the combination of pegylated interferon and ribavirin for 24 or 48 weeks was a remarkable accomplishment of the past decade. However, sustained virological responses rates of about 80% (genotypes 2-3) and 50% (genotype 1) were not satisfactory especially for patients infected with genotype 1. Important advances in the
biology of HCV have made possible the development of the direct-acting antiviral agents boceprevir and telaprevir with substantial increase in the rates of sustained virological response with shorter duration of therapy for a large number of patients. However, the complexity of triple therapy is higher and several new side effects are expected suggesting greater expertise in the patient management. Anemia and disgeusia are frequent with boceprevir while cutaneous rash, ranging from mild to severe, is expected with telaprevir. Higher risk of drug-drug interactions demand further clinical consideration of the previous well-known adverse events of pegylated interferon and ribavirin. Identification and prompt management of these potential new problems with boceprevir and telaprevir are crucial in clinical practice for optimizing treatment and assuring safety outcomes to HCV-genotype 1 patients.


BACKGROUND & AIMS: Formal Hepatitis C virus (HCV) education improves HCV knowledge but the impact on treatment uptake and outcome is not well described. We aimed to evaluate the impact of formal HCV patient education on primary provider-specialist HCV comanagement and treatment. METHODS: Primary care providers within the San Francisco safety-net health care system were surveyed and the records of HCV-infected patients before and after institution of a formal HCV education class by liver specialty (2006-2011) were reviewed retrospectively. RESULTS: Characteristics of 118 patients who received anti-HCV therapy were: mean age 51, 73% males and ~50% White and uninsured. The time to initiation of HCV treatment was shorter among those who received formal education (median 136 vs 284 days, P < 0.0001). When controlling for age, gender, race and HCV viral load, non-1 genotype (OR 6.17, 95% CI 2.3-12.7, P = 0.0003) and receipt of HCV education (OR 3.0, 95% CI 1.1-7.9, P = 0.03) were associated with sustained virologic treatment response. Among 94 provider respondents (response rate = 38%), mean age was 42, 62% were White, and 63% female. Most providers agreed that the HCV education class increased patients' HCV knowledge (70%), interest in HCV treatment (52%), and provider-patient communication (56%). A positive provider attitude (Coef 1.5, 95% CI 0.1-2.9 percent, P = 0.039) was independently associated with referral rate to education class. CONCLUSIONS: Formal HCV education expedites HCV therapy and improves virologic response rates. As primary care provider attitude plays a significant role in referral to HCV education class, improving provider knowledge will likely enhance access to HCV specialty services in the vulnerable population.


GOALS: To describe current hepatitis C virus (HCV) treatment practices in the United States and identify physician characteristics associated with the use of first generation direct-acting antivirals (DAAs). BACKGROUND: HCV treatment practice patterns have not been assessed after the introduction of DAA, which are now considered standard of care for most HCV genotype 1 patients. STUDY: We sampled nationally representative physicians treating HCV patients with DAAs through a web-based survey. Stepwise multivariate logistic regression was
performed to identify physician characteristics associated with the use of DAAs in 4 clinical vignettes (early stage fibrosis, prior null response, human immunodeficiency virus (HIV) co-infection, and post-liver transplantation). **RESULTS:** Of 1658 deliverable emails, 337 (20.3%) clinicians responded. Fifty percent of providers recommended DAA therapy for treatment-naive patients with early stage fibrosis, whereas 49% of providers would await new therapies. For prior null responders with significant fibrosis, 74% would attempt retreatment using DAAs and 26% would await new therapies. Off-label use of DAAs was recommended by 69% of providers for patients with HIV infection and 48% of providers for post-liver transplant patients. Academic affiliation was significantly associated with higher rates of off-label use in both HIV and post-liver transplant patients. **CONCLUSIONS:** Despite more potent and less toxic therapies on the horizon, many physicians recommended DAAs in treatment-naive patients with early stage fibrosis. Providers also frequently recommended DAAs for off-label uses, such as treating post-liver transplant patients and those coinfected with HIV.

**Liver Cancer**


**BACKGROUND:** Liver cirrhosis is the most important risk factor for hepatocellular carcinoma (HCC) but the role of liver disease aetiology in cancer development remains under-explored. We investigated global gene expression profiles from HCC arising in different liver diseases to test whether HCC development is driven by expression of common or different genes, which could provide new diagnostic markers or therapeutic targets. **METHODOLOGY AND PRINCIPAL FINDINGS:** Global gene expression profiling was performed for 4 normal (control) livers as well as 8 background liver and 7 HCC from 3 patients with hereditary haemochromatosis (HH) undergoing surgery. In order to investigate different disease phenotypes causing HCC, the data were compared with public microarray repositories for gene expression in normal liver, hepatitis C virus (HCV) cirrhosis, HCV-related HCC (HCV-HCC), hepatitis B virus (HBV) cirrhosis and HBV-related HCC (HBV-HCC). Principal component analysis and differential gene expression analysis were carried out using R Bioconductor. Liver disease-specific and shared gene lists were created and genes identified as highly expressed in hereditary haemochromatosis HCC (HH-HCC) were validated using quantitative RT-PCR. Selected genes were investigated further using immunohistochemistry in 86 HCC arising in liver disorders with varied aetiology. Using a 2-fold cut-off, 9 genes were highly expressed in all HCC, 11 in HH-HCC, 270 in HBV-HCC and 9 in HCV-HCC. Six genes identified by microarray as highly expressed in HH-HCC were confirmed by RT qPCR. Serine peptidase inhibitor, Kazal type 1 (SPINK1) mRNA was very highly expressed in HH-HCC (median fold change 2291, p=0.0072) and was detected by immunohistochemistry in 91% of HH-HCC, 0% of HH-related cirrhotic or dysplastic nodules and 79% of mixed-aetiology HCC. **CONCLUSION:** HCC, arising from diverse backgrounds, uniformly over-express a small set of genes. SPINK1, a secretory trypsin inhibitor, demonstrated potential as a diagnostic HCC marker and should be evaluated in future studies.

**PURPOSE:** Statins may have protective effects against cancer, but no studies have focused on their effects in patients with chronic hepatitis C virus (HCV) infection. The purpose of this study was to investigate the association between use of statins and risk of hepatocellular carcinoma (HCC) in HCV-infected patients. **PATIENTS AND METHODS:** Ours was a population-based cohort study of 260,864 HCV-infected patients enrolled in the Taiwan National Health Insurance Research Database since January 1, 1999, and observed through December 31, 2010. Cox proportional hazards regression with time-dependent covariates for drug exposures was employed to evaluate the association between statin use and HCC risk. **RESULTS:** There were 27,883 cases of HCC in the HCV cohort during a follow-up period of 2,792,016.6 person-years. Among the 35,023 patients using statins (defined as ≥ 28 cumulative defined daily doses [cDDDs]), 1,378 had HCC. Among the 225,841 patients not using statins (< 28 cDDDs), 26,505 were diagnosed with HCC. A dose-response relationship between statin use and HCC risk was observed. The adjusted hazard ratios were 0.66 (95% CI, 0.59 to 0.74), 0.47 (95% CI, 0.40 to 0.56), and 0.33 (95% CI, 0.25 to 0.42) for patients with 28 to 89, 90 to 180, and > 180 cDDDs per year, respectively, relative to nonusers. The reduction in risk also demonstrated a progressive duration-response relationship in patients with ≥ 28 cDDDs per year when compared with nonusers. **CONCLUSION:** Among patients with HCV infection, statin use was associated with reduced risk of HCC. Further research is needed to elucidate the mechanism responsible for this effect.


Hepatocellular carcinoma (HCC) is the third-leading cause of cancer-related mortality worldwide. Although hepatitis B still remains the most common risk factor worldwide, chronic hepatitis C virus (HCV) infection is the driving force for the increased incidence of HCC especially in Western countries and Japan. In hepatitis B virus (HBV)-endemic areas, after successful vaccination programs against HBV, chronic HCV infection is now emerging as an important cause of chronic liver diseases. Unlike patients with chronic hepatitis B, those with chronic hepatitis C (CHC) develop HCC in the presence of established cirrhosis in most cases. However, a significant minority of CHC develops HCC in the absence of cirrhosis. Although HCV is a RNA virus with little potential for integrating its genetic material into host genome, various HCV proteins, including core, envelope, and nonstructural proteins, have oncogenic properties by inducing oxidative stress, disturbing cellular regulatory pathways associated with proliferation and apoptosis, and suppressing host immune responses. Overall, a combination of virus-specific, host genetic, environmental, and immune-related factors are likely to determine progression to HCC. Strategies aimed at eliminating the virus may provide opportunities for effective prevention of the development of HCC. Pegylated interferon plus ribavirin therapy appears to be effective at reducing the risk of HCC in patients who achieve sustained virologic responses. **In summary,** with the emerging importance of CHC, mechanisms of HCV-associated hepatocellular carcinogenesis should be clarified to provide insight into advanced therapeutic and preventive approaches, which eventually decrease the incidence and mortality of HCC.

BACKGROUND AND AIMS: Tremelimumab is a monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), an inhibitory co-receptor that interferes with T cell activation and proliferation. The purpose of this pilot clinical trial was to test the antitumor and antiviral effect of Tremelimumab in patients with hepatocellular carcinoma (HCC) and chronic hepatitis C virus (HCV) infection; and to study the safety of its administration to cirrhotic patients. METHODS: Tremelimumab at a dose of 15 mg/kg IV every 90 days was administered until tumor progression or severe toxicity. Twenty patients were evaluable for toxicity and viral response and 17 were evaluable for tumor response. Most patients were in the advanced stage and 43% had an altered liver function (Child-Pugh class B). RESULTS: A good safety profile was recorded and no patient needed steroids because of severe immune-mediated adverse events. Some patients had a transient albeit intense elevation of transaminases after the first dose but not following subsequent cycles. Partial response rate was 17.6% and disease control rate was 76.4%. Time to progression was 6.48 months (95% CI 3.95 to 9.14). A significant drop in viral load was observed while new emerging variants of the hypervariable region 1 of HCV replaced the predominant variants present before therapy, particularly in those patients with a more prominent drop in viral load. This antiviral effect was associated with an enhanced specific anti-HCV immune response. CONCLUSIONS: Tremelimumab safety profile and antitumor and antiviral activity in patients with advanced HCC developed on HCV-induced liver cirrhosis support further investigation.


AIM: Vascular endothelial growth factor (VEGF) is a primary driving force for both physiological and pathological angiogenesis, and its overexpression has been found in hepatocellular carcinoma (HCC). The aim of this study was to retrospectively clarify the usefulness of serum VEGF levels as a tumor marker in patients with hepatitis C virus (HCV)-related liver cirrhosis (CLC) and HCC. MATERIALS AND METHODS: The patients with CLC were divided into three groups: 28 patients without HCC (CLC group), 11 patients with HCC (HCC group), and 48 patients with advanced HCC (aHCC group). The control group consisted of 37 patients with chronic HCV. RESULTS: When the relation of serum VEGF to liver function was assessed, there was no significant difference of VEGF levels between the control group and the CLC group. When serum VEGF levels were assessed in relation to the presence of HCC, the VEGF levels of the HCC group and aHCC group were found to be significantly higher than that of the control group, while there was no significant difference between the control group and the CLC group. For the detection of cancer, serum VEGF had the largest area under the curve (AUC) and the highest accuracy when we employed the cut-off value obtained by receiver operating characteristic (ROC) analysis using the Youden index. Evaluation of various tumor markers in the aHCC group showed that the serum levels of α-fetoprotein (AFP) were higher in patients with infiltrating tumors than in patients with multiple
discrete nodules or confluent multinodular tumors, while there were no significant differences in the serum levels of VEGF, Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), and des-γ-carboxy prothrombin. There were no significant differences on the serum levels of all four markers between tumor stages, but serum VEGF was higher in patients with vascular invasion than in those without vascular invasion. **CONCLUSION:** The present findings suggest that the serum levels of VEGF might be a useful predictor of the presence of HCC in patients with CLC, while serum levels of AFP and VEGF can predict the tumor type and vascular invasion, respectively.