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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Reactivation of herpesvirus in patients with hepatitis C treated with direct-acting antiviral agents.

BACKGROUND: We performed a case-series analysis of reactivation of herpesvirus in patients with hepatitis C virus (HCV) infection treated with direct-acting antiviral (DAA) agents. **METHODS:** Eight cases were detected among 100 treated patients with DAA regimens in Qena University Hospital from June 2016 to June 2017. Herpesvirus was reactivated in eight patients who received DAA therapy. None of the cases had risk factor for herpes zoster reactivation. **RESULTS:** The DAA regimens used were sofosbuvir/daclatasvir in six cases and sofosbuvir/ledipasvir in two cases. Immune changes that follow HCV clearance might lead to reactivation of other viruses, such as herpesvirus. **CONCLUSION:**
Patients with HCV infection suspected of having herpesvirus infection should be treated promptly.

Rapid decline of noninvasive fibrosis index values in patients with hepatitis C receiving treatment with direct-acting antiviral agents.

BACKGROUND: Studies on temporal changes in noninvasive fibrosis indices and liver stiffness measurement (LSM) in patients with chronic hepatitis C (CHC) treated with direct-acting antiviral agents (DAAs) are limited. **METHODS:** We retrospectively enrolled consecutive patients with CHC who had received DAAs. **RESULTS:** In total, we recruited 395 consecutive patients, of which 388 (98.2%) achieved a sustained virologic response (SVR) at 12 weeks after therapy. In patients who received DAA therapy and achieved SVR 12 weeks after therapy (n = 388), the median aspartate aminotransferase/platelet ratio index (APRI) value decreased from 1.19 (0.62-2.44) at baseline to 0.50 (0.32-0.95), 0.51 (0.31-0.92), 0.48 (0.31-0.88), and 0.52 (0.33-0.92) at week 2, week 4, end of therapy, and PW12, respectively (all $P < 0.001$). The median FIB-4 value decreased from 2.88 (1.56-5.60) at baseline to 2.10 (1.30-3.65), 2.15 (1.30-3.65), 2.11 (1.37-3.76), and 2.22 (1.45-3.82) at week 2, week 4, end of therapy, and PW12, respectively (all $P < 0.001$). The median alanine aminotransferase level significantly decreased from week 2 until PW12 (all $P < 0.001$). The platelet count significantly increased from 2 weeks after DAA therapy initiation until PW12 (all $P < 0.001$); however, the magnitude of changes in the platelet count was low. In patients with paired LSMs obtained using acoustic radiation force impulse elastography at baseline and PW12 (n = 199), the median LSM decreased

from 1.78 (1.25-2.30) m/s at baseline to 1.38 (1.14-1.88) m/s at PW12 ($P < 0.001$). **CONCLUSIONS:** Noninvasive fibrosis indices, namely APRI and FIB-4, exhibited a rapid and sustained decline from week 2 until PW12 in patients with CHC who achieved SVR to DAA therapy. The rapid decline in APRI and FIB-4 values might mainly result from improvement in necroinflammation

Primary care provider perceptions and experiences of implementing hepatitis C virus birth cohort testing: a qualitative formative evaluation.

BACKGROUND: In 2014, the Department of Veterans Affairs (VA) adopted a screening test policy for hepatitis C virus (HCV) in all "Baby Boomers" - those born between 1945 and 1965. About 1 in 12 Veterans were estimated to be infected with HCV yet approximately 34% of the birth cohort remained untested. Early HCV diagnosis and successful antiviral treatment decrease the risk of onward transmission, cirrhosis, hepatocellular carcinoma, liver transplant, and death. Implementing evidence-based HCV screening in primary care has great potential to reduce morbidity and mortality. To inform design and implementation of a quality improvement intervention, we studied primary care provider (PCP) perceptions of and experiences with HCV birth cohort testing. **METHODS:** We conducted a formative evaluation using qualitative semi-structured interviews guided by the integrated Promoting Action on Research Implementation in Health Services (i-PARIHS) framework. Twenty-two PCPs in six states across a large integrated US healthcare system were interviewed. Content analysis with a priori and emergent codes was performed on verbatim interview transcripts. **RESULTS:** We identified three themes related to primary care provider HCV testing and linkage practices, as mapped to i-PARIHS constructs: 1) evaluating cues to HCV testing (innovation/evidence), 2) framing HCV testing decisions (recipients), and 3) HCV testing and linkage to care in the new treatment era (context). The most frequently reported HCV testing cue was an electronic clinical reminder alert, followed by clinical markers and the presence of behavioral risk factors. Most PCPs saw testing as routine, but less urgent, leading to some reluctance. Providers largely saw themselves as performing guideline-concordant testing, yet no performance data were available to assess performance. Given the recent availability of new HCV medications, many PCPs were highly motivated to test and link patients to specialty care for treatment. **CONCLUSIONS:** Our results suggest a multi-component intervention around awareness and education, feedback of performance data, clinical reminder updates, and leadership support, would address both a significant need, and be deemed acceptable and feasible to primary care providers.

Longitudinal assessment of the association between implementation strategy use and the uptake ofhepatitis C treatment: Year 2.

BACKGROUND: To increase the uptake of evidence-based treatments for hepatitis C (HCV), the Department of Veterans Affairs (VA) established the Hepatitis Innovation Team (HIT) Collaborative. Teams of providers were tasked with choosing implementation strategies to improve HCV care. The aim of the current evaluation was to assess how site-level implementation strategies were associated with HCV treatment initiation and how the use of implementation strategies and their association with HCV treatment changed over time. **METHODS:** A key HCV provider at each VA site ($N = 130$) was asked in two consecutive fiscal years (FYs) to complete an online survey examining the use of 73 implementation strategies organized into nine clusters as described by the Expert Recommendations for

Implementing Change (ERIC) study. The number of Veterans initiating treatment for HCV, or "treatment starts," at each site was captured using national data. Providers reported whether the use of each implementation strategy was due to the HIT Collaborative. **RESULTS:** Of 130 sites, 80 (62%) responded in Year 1 (FY15) and 105 (81%) responded in Year 2 (FY16). Respondents endorsed a median of 27 (IQR19-38) strategies in Year 2. The strategies significantly more likely to be chosen in Year 2 included tailoring strategies to deliver HCV care, promoting adaptability, sharing knowledge between sites, and using mass media. The total number of treatment starts was significantly positively correlated with total number of strategies endorsed in both years. In Years 1 and 2, respectively, 28 and 26 strategies were significantly associated with treatment starts; 12 strategies overlapped both years, 16 were unique to Year 1, and 14 were unique to Year 2. Strategies significantly associated with treatment starts shifted between Years 1 and 2. Pre-implementation strategies in the "training/educating," "interactive assistance," and "building stakeholder interrelationships" clusters were more likely to be significantly associated with treatment starts in Year 1, while strategies in the "evaluative and iterative" and "adapting and tailoring" clusters were more likely to be associated with treatment starts in Year 2. Approximately half of all strategies were attributed to the HIT Collaborative. **CONCLUSIONS:** These results suggest that measuring implementation strategies over time is a useful way to catalog implementation of an evidence-based practice over time and across settings.

Comparison of Compliance and Efficacy of Pegylated Interferon α-2a and α-2b in Adults with Chronic Hepatitis C.

This study compares treatment completion rates and outcomes in hepatitis C virus (HCV) patients between those aged <60 and ≥60 years receiving pegylated interferon (PEG-IFN) α-2a or α-2b combined with ribavirin. No significant differences were found in treatment completion rates and virological responses between age-stratified patients or between genotype-stratified patients receiving PEG-IFN α-2a versus PEG-IFN α-2b. Significantly more patients ≥60 years of receiving PEG-IFN α-2b exhibited an early virological response compared to those receiving PEG-IFN α-2a ($P = 0.002$); for patients <60 years of age, treatment outcomes were similar between the 2 groups. More liver fibrosis was observed in patients with HCV of genotype 1 than in those with genotypes 2 or 3. Mean changes in pre- and post-treatment fibrosis variables (bilirubin, platelet count, liver enzymes, FIB-4, and APRI) in HCV genotype 1 patients were greater in those receiving PEG-IFN α-2b than in those receiving PEG-IFN α-2a. Significant differences were not observed between age- and HCV genotype-stratified patients receiving PEG-IFN α-2a and -α-2b, but α-2b appears to have a modest efficacy advantage over α-2b, particularly in male HCV patients ≥60 years of age.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Hepatitis C Virus Infection: Host¯Virus Interaction and Mechanisms of Viral Persistence.

Hepatitis C (HCV) is a major cause of liver disease, in which a third of individuals with chronic HCV infections may develop liver cirrhosis. In a chronic HCV infection, host immune factors along with the actions of HCV proteins that promote viral persistence and dysregulation of the immune system have an impact on immunopathogenesis of HCV-induced hepatitis. The genome of HCV encodes a single polyprotein, which is translated and processed into structural and nonstructural proteins. These HCV proteins are the target of the innate and adaptive immune system of the host. Retinoic acid-inducible gene-I (RIG-I)-like receptors and Toll-like receptors

are the main pattern recognition receptors that recognize HCV pathogen-associated molecular patterns. This interaction results in a downstream cascade that generates antiviral cytokines including interferons. The cytolysis of HCV-infected hepatocytes is mediated by perforin and granzyme B secreted by cytotoxic T lymphocyte (CTL) and natural killer (NK) cells, whereas noncytolytic HCV clearance is mediated by interferon gamma (IFN-γ) secreted by CTL and NK cells. A host-HCV interaction determines whether the acute phase of an HCV infection will undergo complete resolution or progress to the development of viral persistence with a consequential progression to chronic HCV infection. Furthermore, these host-HCV interactions could pose a challenge to developing an HCV vaccine. This review will focus on the role of the innate and adaptive immunity in HCV infection, the failure of the immune response to clear an HCV infection, and the factors that promote viral persistence.

The Role of ApoE in HCV Infection and Comorbidity.

Hepatitis C virus (HCV) is an RNA virus that can efficiently establish chronic infection in humans. The overlap between the HCV replication cycle and lipid metabolism is considered to be one of the primary means by which HCV efficiently develops chronic infections. In the blood, HCV is complex with lipoproteins to form heterogeneous lipo-viro-particles (LVPs). Furthermore, apolipoprotein E (ApoE), which binds to receptors during lipoprotein transport and regulates lipid metabolism, is localized on the surface of LVPs. ApoE not only participate in the attachment and entry of HCV on the cell surface but also the assembly and release of HCV viral particles from cells. Moreover, in the blood, ApoE can also alter the infectivity of HCV and be used by HCV to escape recognition by the host immune system. In addition, because ApoE can also affect the antioxidant and immunomodulatory/anti-inflammatory properties of the host organism, the long-term binding and utilization of host ApoE during chronic HCV infection not only leads to liver lipid metabolic disorders but may also lead to increased morbidity and mortality associated with systemic comorbidities.

Chronic Hepatitis C Virus Infection Impairs M1 Macrophage Differentiation and Contributes to CD8+ T-Cell Dysfunction.

Chronic hepatitis C virus (HCV) infection causes generalized CD8+ T cell impairment, not limited to HCV-specific CD8+ T-cells. Liver-infiltrating monocyte-derived macrophages (MDMs) contribute to the local micro-environment and can interact with and influence cells routinely trafficking through the liver, including CD8+ T-cells. MDMs can be polarized into M1 (classically activated) and M2a, M2b, and M2c (alternatively activated) phenotypes that perform pro- and anti-inflammatory functions, respectively. The impact of chronic HCV infection on MDM subset functions is not known. Our results show that M1 cells generated from chronic HCV patients acquire M2 characteristics, such as increased CD86 expression and IL-10 secretion, compared to uninfected controls. In contrast, M2 subsets from HCV-infected individuals acquired M1-like features by secreting more IL-12 and IFN-γ. The severity of liver disease was also associated with altered macrophage subset differentiation. In co-cultures with autologous CD8+ T-cells from controls, M1 macrophages alone significantly increased CD8+ T cell IFN-γ expression in a cytokine-independent and cell-contact-dependent manner. However, M1 macrophages from HCV-infected individuals significantly decreased IFN-γ expression in CD8+ T-cells. Therefore, altered M1 macrophage differentiation in chronic HCV infection may contribute to observed CD8+ T-cell dysfunction. Understanding the immunological perturbations

in chronic HCV infection will lead to the identification of therapeutic targets to restore immune function in HCV+ individuals, and aid in the mitigation of associated negative clinical outcomes.

Daclatasvir, sofosbuvir with or without ribavirin for 24 weeks in hepatitis C genotype 3 cirrhosis: A real-life study.

INTRODUCTION AND AIM: Cirrhotic patients with hepatitis C virus genotype 3 infection show unsatisfactory outcomes after 12 weeks' treatment with direct antiviral agents. The National Italian Drug Agency allows 24 weeks of therapy in difficult-to-treat patients, including genotype 3 cirrhotics. Aim of this study was to evaluate efficacy and safety of a 24-week course of sofosbuvir plus daclatasvir±ribavirin in this population. **MATERIALS AND METHODS:** 106 consecutive cirrhotics (70.8% males, mean age 55.3±7.6 years) in 8 tertiary hepatology centers received sofosbuvir plus daclatasvir for 24 weeks. Ribavirin was administered in 85 (80.2%) based expected tolerability, at a mean dose of 964±202mg/day. Baseline Child-Pugh class was A 91.5%, B 6.6%, C 1.9%; mean baseline MELD was 8.5±2.7. RESULTS:
All patients completed 12-week follow-up post-treatment, and 104 (98.1%) obtained sustained virological response (100% in ribavirin -treated patients vs. 90.4% without ribavirin; p=0.04). No worsening in renal and liver function was observed, no serious adverse events occurred. Two virological failures showed resistance associated variants (Y93H and S282T). **CONCLUSION:** An extended 24-week treatment with sofosbuvir plus daclatasvir+ribavirin obtained 100% efficacy in genotype 3 hepatitis C cirrhosis, with very limited side effects. The role of ribavirin seems crucial in this setting and should be administered if clinically feasible.

A systematic review with meta-analysis: Is ribavirin necessary in sofosbuvir- based direct-acting antiviral therapies for patients with HCV recurrence after liver transplantation?

OBJECTIVES: With the appearance of direct-acting antiviral agents (DAAs), sofosbuvir (SOF)-based DAAs are recommended for patients with hepatitis C virus (HCV) recurrence after liver transplantation (LT). Whether ribavirin (RBV) is needed by patients after LT in combination with SOF-based DAAs remains to be determined. This meta-analysis was conducted to evaluate the necessity of RBV with SOF-based DAAs for post-LT patients. **METHODS:** PubMed, Web of Science, Cochrane Library and EMBASE databases were systematically searched for eligible studies from the databases' inceptions until November 2018. We accepted the studies that included HCV recurrence in post-LT patients who were treated with SOF-based DAAs ± RBV, and evaluated the rate of sustained virological response 12 weeks (SVR12) after the end of treatment. RESULTS: Twelve studies, comprising a total of 1466 L T recipients, were included in this study. The pooled SVR12 of these patients was 91% (95% CI: 84% to 95%). There was no statistical difference of SVR12 in the patients treated with SOF-based DAAs + RBV versus -RBV group (risk ratio [RR] = 0.97; 95% CI: 0.92 to 1.03; P = 0.35) by different therapy duration (P = 0.26), with different targets of DAAs (P = 0.13) and in different regions (P = 0.34) but a tendency for a higher incidence of anemia in the + RBV group than in the -RBV group (RR = 5.18; 95% CI: 3.41 to 7.86; p < 0.00001). **CONCLUSION:** The addition of RBV may not contribute to a higher SVR rate and could increase the incidence of anemia, so RBV is not necessary in SOF-based DAAs for patients with HCV recurrence after LT.

Mutational pathway maps and founder effects define the within-host spectrum of hepatitis C virus mutants resistant to drugs.

Knowledge of the within-host frequencies of resistance-associated amino acid variants (RAVs) is important to the identification of optimal drug combinations for the treatment of hepatitis C virus (HCV) infection. Multiple RAVs may exist in infected individuals, often below detection limits, at any resistance locus, defining the diversity of accessible resistance pathways. We developed a multiscale mathematical model to estimate the pre-treatment frequencies of the entire spectrum of mutants at chosen loci. Using a codon-level description of amino acids, we performed stochastic simulations of intracellular dynamics with every possible nucleotide variant as the infecting strain and estimated the relative infectivity of each variant and the resulting distribution of variants produced. We employed these quantities in a deterministic multi-strain model of extracellular dynamics and estimated mutant frequencies. Our predictions captured database frequencies of the RAV R155K, resistant to NS3/4A protease inhibitors, presenting a successful test of our formalism. We found that mutational pathway maps, interconnecting all viable mutants, and strong founder effects determined the mutant spectrum. The spectra were vastly different for HCV genotypes 1a and 1b, underlying their differential responses to drugs. Using a fitness landscape determined recently, we estimated that 13 amino acid variants, encoded by 44 codons, exist at the residue 93 of the NS5A protein, illustrating the massive diversity of accessible resistance pathways at specific loci. Accounting for this diversity, which our model enables, would help optimize drug combinations. Our model may be applied to describe the within-host evolution of other flaviviruses and inform vaccine design strategies.

Safety and efficacy of glecaprevir/pibrentasvir in patients with chronic hepatitis C genotypes 1-6 receiving opioid substitution therapy.

BACKGROUND: International guidelines recommend treatment of hepatitis C virus (HCV) infection in people who inject drugs (PWID), including those on opioid substitution therapy (OST). The pangenotypic combination of glecaprevir and pibrentasvir has shown high sustained virologic response at post-treatment Week 12 (SVR12) in clinical trials. Herein, we evaluate the safety and efficacy of glecaprevir/pibrentasvir in patients receiving OST. **METHODS:** Pooled data from patients with HCV genotypes 1-6 who were treated with glecaprevir/pibrentasvir for 8, 12, or 16 weeks in eight Phase 2 and 3 trials were categorized by use of OST. Treatment completion, treatment adherence, SVR12, adverse events (AEs), and laboratory abnormalities were evaluated for patients receiving and not receiving OST. **RESULTS:** Among 2256 patients, 157 (7%) were receiving OST. Compared with patients not receiving OST, OST patients were younger (mean age, 46.8 vs 52.8 years), male (69% vs 54%), white (93% vs 80%), HCV treatment-naïve (86% vs 72%), had HCV genotype 3 (60% vs 26%), and had a history of depression or bipolar disorder (43% vs 19%). Most patients completed (OST: 98% [n/N = 154/157]; non-OST: 99% [n/N = 2070/2099]) and were adherent (received ≥90% of study drug doses) to glecaprevir/pibrentasvir treatment (OST: 98% [n/N = 121/123]; non-OST: 99% [n/N = 1884/1905] among patients with available data). In the intention-to-treat population, SVR12 rates in OST and non-OST patients were 96.2% (n/N = 151/157; 95% CI 93.2-99.2) and 97.9% (n/N = 2055/2099; 95% CI 97.3-98.5), respectively. For OST patients, reasons for nonresponse included virologic relapse (<1%; n = 1), premature study drug discontinuation (<1%; n = 1), and loss to follow-up (3%; n = 4). AEs occurring in ≥10% of OST patients were headache, fatigue, and nausea. Drug-related serious AEs, AEs leading to study drug discontinuation, and Grade 3 or higher laboratory abnormalities were infrequent in both

groups (<1%). No HCV reinfections occurred through post-treatment Week 12.
CONCLUSION: Glecaprevir/pibrentasvir is highly efficacious and well tolerated in HCV-infected patients receiving OST.

The Successful Retreatment with Glecaprevir and Pibrentasvir of Genotype 1 or 2 HCV-infected Hemodialysis Patients who Failed to Respond to NS5A and Protease Inhibitor Treatment.
Clinical trials and real-world data have proven that hepatitis C virus (HCV) in most infected patients can be eradicated by direct-acting antivirals (DAAs). However, the proper retreatment regimen for hemodialysis patients with HCV infection who have previously failed to respond to DAAs has not been clarified. We herein report, for the first time, the successful retreatment with glecaprevir and pibrentasvir, of three hemodialysis patients with genotype 1 or 2 HCV infection, who had previously failed to respond to combination therapy with an HCV-NA5A inhibitor (daclatasvir) and an HCV protease inhibitor (asunaprevir).

HIV/HCV COINFECTION

Toward DNA-Based T-Cell Mediated Vaccines to Target HIV-1 and Hepatitis C Virus: Approaches to Elicit Localized Immunity for Protection.
Human immunodeficiency virus (HIV)-1 and hepatitis C virus (HCV) are major contributors to the global disease burden with many experts recognizing the requirement of an effective vaccine to bring a durable end to these viral epidemics. The most promising vaccine candidates that have advanced into pre-clinical models and the clinic to eliminate or provide protection against these chronic viruses are viral vectors [e.g., recombinant cytomegalovirus, Adenovirus, and modified vaccinia Ankara (MVA)]. This raises the question, is there a need to develop DNA vaccines against HIV-1 and HCV? Since the initial study from Wolff and colleagues which showed that DNA represents a vector that can be used to express transgenes durably in vivo, DNA has been regularly evaluated as a vaccine vector albeit with limited success in large animal models and humans. However, several recent studies in Phase I-IIb trials showed that vaccination of patients with recombinant DNA represents a feasible therapeutic intervention to even cure cervical cancer, highlighting the potential of using DNA for human vaccinations. In this review, we will discuss the limitations and the strategies of using DNA as a vector to develop prophylactic T cell-mediated vaccines against HIV-1 and HCV. In particular, we focus on potential strategies exploiting DNA vectors to elicit protective localized CD8+ T cell immunity in the liver for HCV and in the cervicovaginal mucosa for HIV-1 as localized immunity will be an important, if not critical component, of an efficacious vaccine against these viral infections.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Hepatitis C Virus Potentially Transmitted by Opioid Drug Diversion from a Nurse - Washington, August 2017-March 2018.

During January 22-March 23, 2018, a local health department in Washington was notified of two patients who received a diagnosis of acute hepatitis C virus (HCV) infection. Neither patient had behavioral risk factors associated with HCV acquisition; however, both had received injectable narcotic (opioid) drugs from the same nurse during separate visits to an emergency department (ED) at a local hospital on December 6 and December 16, 2017. Investigation revealed that the nurse had accessed the automated drug dispensing system at a higher frequency than had other staff members, admitted diverting* patients' injectable narcotic and antihistamine drugs for personal use, and tested positive for HCV antibodies (anti-HCV) on March 19, 2018, but did not have quantifiable HCV RNA. Specimens from both patients were sent to CDC for genetic testing, and HCV viral variants analysis found a significant level of genetically similar HCV variants in both patients, indicating a common source of infection. Further investigation was conducted to confirm the infection source, identify other potentially exposed patients, and treat any new patients who received an HCV diagnosis. Monitoring frequency of access to drug dispensing systems can help identify staff members with abnormal dispensing patterns, including diversion activities (1). U.S. health care facilities are required to prevent, identify, and report any loss, diversion, or theft of controlled substances (2).

Integrated care of severe infectious diseases to people with substance use disorders; a systematic review.

BACKGROUND: Various integrated care models have been used to improve treatment completion of medications for chronic hepatitis B virus (HBV), chronic hepatitis C virus (HCV), Mycobacterium tuberculosis (TB), and Human immunodeficiency virus (HIV) among people with substance use disorders (SUD). We have conducted a systematic review to evaluate whether integrated models have impacts of the treatment of infectious diseases among marginalized people with SUD. **METHODS:** We searched MEDLINE/PubMed (1946 to 2018, on July 26, 2018) and Embase (from 1974 to 2018, on July 26, 2018) for randomized controlled trials (RCTs) and cohort studies evaluating diverse integrated models' effects on sustained virological response (SVR), HIV suppression, HBV curation or suppression, completion of TB treatment regimen among people with SUD. The included studies were assessed qualitatively**. RESULTS**: Altogether, 1640 studies, and references to 1135 related reviews and RCTs were considered, and only seven RCTs and three cohort studies fulfilled the inclusion criteria. We identified nine integrated care models. Two studies, one RCT and one cohort study, showed a significant effect of their integrated models. The RCT evaluated psychosocial treatment, opioid agonist treatment (OAT) and directly observed TB treatment, and found a significant increase in TB treatment completions among intervention group compared to control group (60% versus 13%, $p < 0.01$). The cohort study including OAT and TB treatments had an effect on TB treatment completion in hospitalized patients (89% versus 73%, $p = 0.03$). Eight out of ten studies showed no significant effects of their integrated care models on defined outcomes. One of which having included 363 participants in a RCT showed no effect on SVR compared to the control group when the results adjusted for active substance use and alcohol dependence in a post-hoc analysis (11% versus 7%, $p = 0.49$) **CONCLUSIONS:** The findings indicate uncertainty on the effects of integrated care models' on treatment for severe infectious diseases among people with SUD. Some studies point

toward that integrated models could improve care of people with SUD, yet high-quality studies and preferably, sufficiently sized clinical trials are needed to conclude on the degree of impact.

The change in liver stiffness, controlled attenuation parameter and fibrosis-4 index for chronichepatitis C patients with direct-acting antivirals.

BACKGROUND AND AIM: Transient elastography and fibrosis-4 index (FIB-4) have been proposed to access hepatic fibrosis and steatosis for patients with chronic liver disease. This study was to determine the changes of liver stiffness (LS), controlled attenuation parameter (CAP) value and FIB-4 and their associated factors for chronic hepatitis C (CHC) patients who underwent direct-acting antivirals (DAAs). **PATIENTS AND METHODS:** Consecutive patients with CHC in advanced fibrosis or compensated cirrhosis undergoing paritaprevir/ritonavir/ombitasvir plus dasabuvir therapy and with LS and CAP before and 12 weeks after treatment were enrolled. The demographics, clinical characteristics and treatment outcomes were reviewed. The changes of LS, FIB-4, CAP and their associated factors were analyzed. RESULTS: A total of 213 patients (mean age: 63.7 years) with complete recommended treatment were enrolled. All patients achieved sustained virological response at 12 weeks (SVR12) of follow-up. The mean values of LS, CAP and FIB-4 index before treatment were 18.5kPa, 283dB/m and 5.05 respectively. While there was no significant change in CAP, LS and FIB-4 decreased significantly at the time of SVR12 ($p<0.001$). Compared with follow-up period, LS and FIB-4 decreased rapidly during DDAs. Multivariate analysis showed that higher baseline LS and FIB-4 were associated with greater reductions at the time of SVR12. **CONCLUSION**:For CHC patients in advanced fibrosis or compensated cirrhosis, DAAs improved LS and FIB-4 index at SVR12. Higher baseline LS and FIB-4 contributed to greater reductions. However, there was no significant change in CAP value.

Improving engagement with healthcare in hepatitis C: a randomised controlled trial of a peer support intervention.

BACKGROUND: Peer support can enable patient engagement with healthcare services, particularly for marginalised populations. In this randomised controlled trial, the efficacy of a peer support intervention at promoting successful engagement with clinical services for chronic hepatitis C was assessed. **METHODS**: In London, UK, potential participants were approached through outreach services for problematic drug use and homelessness. Individuals positive for hepatitis C virus (HCV) after confirmatory testing were randomised using an online service to the intervention (peer support) or standard of care. The primary outcome of interest was successful engagement with clinical hepatitis services. The study was non-blinded. Absolute differences were calculated using a generalised linear model and the results compared to logistic regression. **RESULTS**: Three hundred sixty-four individuals consented to participate. One hundred one had chronic hepatitis C and were randomised, 63 to receive the intervention (peer support). A successful outcome was achieved by 23 individuals in this arm (36.5%) and seven (18.4%) receiving the standard of care, giving an absolute increase of 18.1% (95% confidence interval 1.0-35.2%, p value = 0.04). This was mirrored in the logistic regression (odds ratio 2.55 (0.97-6.70), p = 0.06). No serious adverse events were reported. **CONCLUSIONS:** Peer support can improve the engagement of patients with chronic HCV with healthcare services.

HEPATOCELLULAR (LIVER) CANCER

Alpha-fetoprotein to transaminase ratio is related to higher diagnostic efficacy for hepatocellular carcinoma.

Alpha-fetoprotein (AFP), as the most widely used biomarker of hepatocellular carcinoma (HCC), was correlated with ongoing liver damage. The aim of this study was to evaluate the ability of inflammatory correction-based AFP to identify HCC from other liver diseases.From March 2012 to March 2017, among 926 participants, a total of 501 patients whose transaminases were higher than the upper limit of normal range, including 166 treatment-naïve HCC patients were enrolled in our retrospective study. The liver function, white blood cell (WBC) count and serum AFP level of all patients were collected at the initial stage of admission. The area under the receiver-operating curve (AUROC) of AFP, AFP/(Aspartate aminotransferase*Alanine aminotransferase) [AFP/(AST*ALT)] and AFP/WBC were compared between the HCC group and the control groups for the quantifying diagnostic efficacy.AUROCs of our novel index AFP/(AST*ALT) were up to 0.853 (95% confidence interval, CI 0.818-0.887, P<.001) and 0.825 (95% CI 0.782-0.868, P<.001), respectively, when differentiating HCC from non-HCC patients and from cirrhosis patients, which was superior to AFP and AFP/WBC. Diagnostic performance of AFP/(AST*ALT) could be verified in hepatitis B virus (HBV)- or hepatitis C virus (HCV)-associated HCC patients as well. What's more, AFP/(AST*ALT) had a significant positive and moderate correlation with tumor diameter and presence of cancerous emboli or not (Spearman correlation coefficients were 0.323 and 0.305, respectively; both P<.001). For predicting HCC, the optimal cut-off value of AFP/(AST*ALT) is 1.603, and the sensitivity and specificity were 82.8% and 72.7%, respectively, which were significantly higher than the AFP and AFP/WBC.The serum AFP levels based on correction of liver inflammation can effectively improve the diagnostic performance of HCC, providing a new indicator that is simple, economical and pervasive for clinic.

Mac-2 Binding Protein Glycosylation Isomer as a Hepatocellular Carcinoma Marker in Patients With Chronic Hepatitis B or C Infection.

Mac-2 binding protein glycosylation isomer (M2BPGi) is a novel glycoprotein biomarker that correlates with liver fibrosis. It has been investigated in East Asian populations as a hepatocellular carcinoma (HCC) biomarker. We assessed M2BPGi as an HCC biomarker in an ethnically diverse cohort of patients with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. We enrolled 947 treatment-naive patients mono-infected with HBV or HCV without HCC at baseline. Biomarker levels were measured from baseline sera and correlated with longitudinal clinical data. The primary outcome was HCC occurrence during long-term follow-up. Median M2BPGi was significantly higher among patients with cirrhosis (2.67 versus 0.80; P < 0.001) and patients who developed HCC (3.22 versus 1.16; P < 0.001). The area under the receiver operating characteristic (AUROC) for M2BPGi and alpha-fetoprotein (AFP) was similar overall (0.77 versus 0.72; P = 0.15), but M2BPGi outperformed AFP among patients with HBV (0.84 versus 0.75; P = 0.02). M2BPGi performed poorly among patients with HCV (AUROC, 0.51). M2BPGi was an independent predictor of HCC among patients with HBV but not among patients with HCV. M2BPGi performed better in patient subgroups with a lower prevalence of cirrhosis. Conclusion: In our HBV cohort, M2BPGi was more effective than AFP in predicting HCC and was an independent predictor of HCC. However, M2BPGi had limited predictive value in our HCV cohort, likely due to a high cirrhosis burden in this cohort. Further studies are needed to evaluate M2BPGi as an HCC biomarker in broader patient populations with more diverse disease etiology, non-Asian ethnicity, and more advanced fibrosis.

Long-term follow-up after cure from chronic hepatitis C virus infection shows occult hepatitis and a risk of hepatocellular carcinoma in noncirrhotic patients.

OBJECTIVES: Curing of hepatitis C virus (HCV) infection primarily aims to prevent severe liver complications. Our objectives were to investigate the long-term presence and impact of occult HCV infection (OCI) and to study the outcomes in terms of liver disease after virological cure. **PATIENTS AND METHODS:** A total of 97 patients with achieved sustained virological response (SVR) during 1990-2005 were followed either by a clinical follow-up (FU) visit with blood sampling and liver elastography (n=54) or through national registries for outcomes (n=43). To diagnose OCI among patients with SVR, a highly sensitive method was used to detect HCV-RNA traces in whole blood. The FU duration was a median of 10.5 years, with samples up to 21.5 years after the end of treatment (EOT). **RESULTS**: The majority of patients [52 (96%)] were HCV-RNA negative at FU, and regression of fibrosis was statistically significant. OCI was found in two (4%) of them at 8 and 9 years after EOT. These patients had F1 and F2 fibrosis before treatment and F2 at FU, but no other abnormal findings. Three previously noncirrhotic men were diagnosed with hepatocellular carcinoma 8-11 years after EOT. **CONCLUSION:** Occult infection could be detected many years after the achievement of SVR but was not associated with serious liver disease. The majority had persistent viral eradication and regression of fibrosis after SVR. However, an increased risk of hepatocellular carcinoma may persist in the long term after SVR even in noncirrhotic patients. Further studies with FU after direct-acting antiviral therapy and on the long-term impact after cure are needed.

Contrast imaging techniques to diagnose hepatocellular carcinoma in cirrhotics outside regular surveillance.

INTRODUCTION AND AIM: The American Association for the Study of the Liver (AASLD) recommends contrast computerized tomography (CT-scan) and magnetic resonance (MRI) to diagnose hepatocellular carcinoma (HCC) arising in cirrhotic patients under semiannual surveillance with abdominal ultrasound (US). A US guided fine needle biopsy (FNB) serves the same purpose in radiologically undiagnosed tumors and incidentally detected nodules in cirrhotics outside surveillance. In this population, we evaluated the performance of radiological diagnosis of HCC according to 2010 AASLD recommendations. **MATERIALS AND METHODS**: All cirrhotic patients with a liver nodule incidentally detected by US were prospectively investigated with a sequential application of CT-scan/MRI examination and a FNB. RESULTS: Between 2011 and 2015, 94 patients (mean age 67 years) had a liver nodule (total 120) detected by US in the context of histologically confirmed cirrhosis. Mean nodules diameter was 40 (10-160) mm, 87 (73%) <5cm. At histology, 84 (70%) nodules were HCC, 8 (7%) intrahepatic cholangiocarcinoma, 6 (5%) metastases, 2 (2%) neuroendocrine tumors and 20 (16%) benign lesions. Hyperenhancement in arterial phase followed by wash-out in venous phases on at least one radiological technique was demonstrated in 62 nodules (61 HCC, 1 high grade dysplastic nodule), with a specificity of 97% (IC95%: 85-100%), sensitivity 73% (IC95%: 62-81%) and diagnostic accuracy 80%, being 64% for ≥5cm HCC. Sensitivity of AFP >200ng/mL was 12% (IC95%: 6-23%). **CONCLUSION:** A single contrast imaging technique showing a typical contrast pattern confidently identifies HCC also in cirrhotic patients with an incidental liver nodule, thereby reducing the need for FNB examinations.

All-trans-retinoic acid (ATRA) plus oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX) versus FOLFOX alone as palliative chemotherapy in patients with advanced hepatocellular carcinomaand extrahepatic metastasis: study protocol for a randomized controlled trial.

BACKGROUND: Among patients with hepatocellular carcinoma (HCC), 85% of patients have an advanced disease stage at diagnosis and curative therapies cannot be performed. Prognosis has been quite poor as until recently there was no proven effective chemotherapy. Our group found that all-trans-retinoic acid (ATRA) could improve the efficacy of platinum in HCC in vivo and in vitro, thus we wish to validate the efficiency of ATRA in clinical practice. METHODS: This is a double-blinded, 1:1 randomized, controlled, multicenter clinical trial. Three hundred and sixty-eight patients with HCC and extrahepatic metastases will receive palliative chemotherapy at the Eastern Hepatobiliary Surgery Hospital, First Hospital of Jilin University and Fujian Provincial Cancer Hospital. Subjects will be randomly assigned to one of the two arms, either ATRA + oxaliplatin + 5-fluorouracil/leucovorin (FOLFOX4) or FOLFOX4 alone. ATRA 20 mg will be given orally three times/day for 3 days prior to the initiation of FOLFOX4. ATRA will be discontinued at the end of FOLFOX4. DISCUSSION: Overall survival rate is the primary endpoint. Secondary endpoints are time to progression according to the modified response evaluation criteria in solid tumors (mRECIST) criteria, acute and chronic adverse events, and quality of life. TRIAL REGISTRATION: Chinese Clinical Trial Registry, ChiCTR-IIR-17012916 . Registered on 9 October 2017.

Preoperative Health-Related Quality of Life Predicts Minimal Clinically Important Difference and Survival after Surgical Resection of Hepatocellular Carcinoma.

Despite the growing use of minimal clinically important difference (MCID) as a cancer outcome measure, no study has reported clinically significant outcomes in cancer patients. We defined MCID and evaluated the use of preoperative HRQoL for predicting MCID and survival after surgical resection of hepatocellular carcinoma (HCC). In total, 369 patients completed the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) and the SF-36 at baseline and at two years post-operative at three tertiary academic hospitals. The corresponding MCID values were 3.6 (SF-36 physical component summary), 4.2 (SF-36 mental component summary), 5.4 (FACT-General total score), and 6.7 (FACT-Hep total score). The predictors of achieving postoperative MCID were significantly higher in patients who had low preoperative HRQoL score, advanced age, high education level, and high BMI ($p < 0.05$). However, patients with a high preoperative HRQoL score, high education level, high BMI, and low Charlson comorbidity index score were significantly associated with survival ($p < 0.05$). Preoperative HRQoL scores were predictive of MCID and overall survival after surgical resection of HCC. The findings of this study may be useful for managing the preoperative expectations of candidates for HCC resection and for developing shared decision-making procedures for patients undergoing surgical resection of HCC.