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ABSTRACTS

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PO-C-01

Post-treatment wisteria floribunda agglutinin-positive Mac-2-binding protein combined with platelet predict hepatocellular carcinoma development in chronic hepatitis C patients

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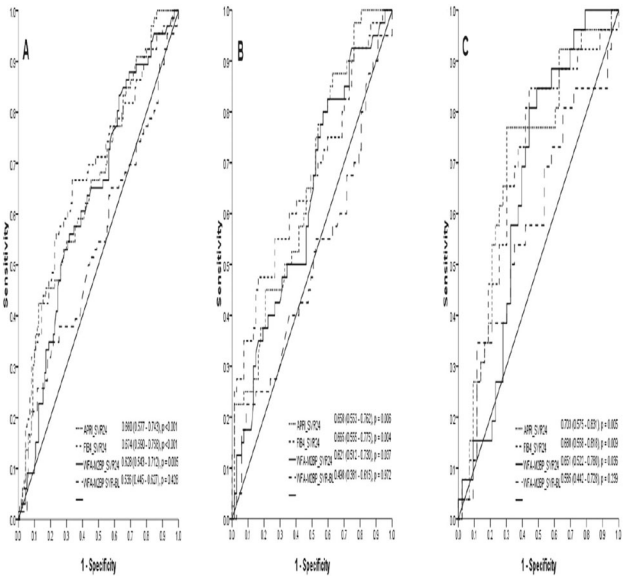
Background: Wisteria floribunda agglutinin-positive Mac-2-binding protein (WFA+-M2BP) is a novel marker for liver fibrosis assessment. We aimed to predict the hepatocellular carcinoma (HCC) occurrence after antiviral therapy in Taiwanese patients with chronic hepatitis C (CHC) using WFA+-M2BP.

Method: Seventy patients with HCC and another 140 age, gender, sustained virological response (SVR) propensity matched, non-HCC patients were recruited. Pre- and 24 weeks post-treatment (SVR24) serum WFA+-M2BP levels were measured. The primary endpoint of the study was whether serum WFA+-M2BP level predicts HCC development.

Result: There was no difference of WFA+-M2BP level at pre-treatment, but a significantly higher WFA+-M2BP level at SVR24 in patients with HCC. The accuracy of WFA+-M2BP at SVR24 in the prediction of HCC was 0.628 (0.543-0.712) in all, 0.621 (0.512-0.730) in patients with SVR, and 0.651 (0.522-0.780) in patients without SVR. Cox-regression hazard analysis demonstrated Platelet (HR 0.99, 95% CI 0.982-0.997, p = 0.005) and WFA+-M2BP at SVR24 (HR 1.11, 95% CI 1.022–1.194, p = 0.012) as independent factors associated with HCC. Combined Platelet and WFA+-M2BP at SVR24, a better predictive ability for HCC development was found in all, and patients with/without HCV SVR24.

Conclusion: Post-treatment WFA+-M2BP, especially combined with platelet, predict HCC development in Taiwanese CHC patients after antiviral therapy.



Result: Current levels of treatment can be maintained by implementing general population screening with 5% of individuals screened annually ($\sim$ 10 million tested/year) and 35% of diagnosed individuals initiating treatment, resulting in 82 tests per treatment and 5 infections averted per 1000 antibody screenings (IA/1000 Ab). However, incidence and mortality will rise by 6% and 38%, respectively, by 2030. Much greater impact is achieved by doubling annual screening to 10%, targeting priority groups with higher prevalence of HCV infection such as PWID and adults (> 20 years), increasing referral rates to 90%, and introducing re-screening every 5 years, with 56 tests per treatment, 10 IA/1000Ab, and the WHO mortality target reached by 2041. However, only with also halving HCV transmission risk in PWID will HCV incidence and mortality approach the WHO targets, now being reached by 2036. Preliminary costing estimates suggest that screening and treatment scale-up in Pakistan is likely to cost about USD$2,000 per cure, with the majority (70%) of costs coming from screening.
Conclusion: Substantial scale-up of screening and treatment interventions will be required to achieve the WHO HCV elimination targets. This can be optimised if targeted strategies are undertaken, but despite this, costs will be substantial.

Session: Hepatitis B Virus Infection- Clinical ; Chairpersons; Baldev Rana; Zaigam Abbas; Shalimar

O-HBV-31

Functional remission of HBeAg negative chronic HBV infection after withdrawal of combined therapy with REP 2139 or REP 2165, tenofovir disoproxil fumarate and pegylated interferon a-2a

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Background: The REP 401 protocol (NCT02565719) is a randomized, controlled trial assessing the safety and efficacy of the nucleic acid polymers REP 2139 (lead clinical candidate) or REP 2165 combined with tenofovir disoproxil fumarate (TDF) and pegylated interferon α-2a (peg-IFN) in treatment naïve Caucasian patients with chronic HBeAg negative HBV infection.
Method: TDF monotherapy (24 weeks, 300 mg PO qD) was followed by randomization into experimental and control groups. Experimental patients received 48 weeks of TDF, peg-IFN (180ug SC qW) and REP 2139 or REP 2165 (250 mg IV infusion qW). Control patients receive 48 weeks of TDF + peg-IFN but crossover to 48 weeks of experimental therapy in the absence of a 3 log drop in HBsAg after 24 weeks of peg-IFN. Viremia is monitored on the Abbott Architect and Realtime platforms.
Result: Currently, 19/20 control patients have been crossed over and have completed $\geq$ 24 weeks of experimental therapy and 19/20 experimental patients have completed treatment and 4-12 weeks of follow-up. Therapy is well tolerated in all except in one crossover patient (REP 2165) who withdrew from therapy due to pegIFN-related depression. Following crossover in the control group, 10/10 patients (REP 2139) and 9/10 patients (REP 2165) have HBsAg reductions > 1 log from baseline. From these 19 responder patients, 14 have achieved HBsAg < 1 IU/mL and 11 have achieved HBsAg $\leq$ 0.01 IU/mL. In the experimental group, 9/10 patients (REP 2139) and 8/10 patients (REP 2165) had HBsAg reductions > 1 log from baseline. From these 17 responder patients, 14 achieved HBsAg < 1 IU/mL and 13 achieved HBsAg $\leq$ 0.01 IU/mL. HBsAg < 1 IU/mL in experimental patients was accompanied by profound increases in anti-HBs (93 to 223,055 mIU/mL) in 9/14 patients and strong therapeutic liver flares (ALT/AST > 5× ULN with normal synthetic liver function) in 12/14 patients. In control patients following crossover to NAP therapy, anti-HBs response is similar (69-68468 mIU/mL), however the strength of liver flares with similar HBsAg reductions were markedly attenuated. Functional remission of HBV infection (HBsAg $\leq$ LLOQ, HBV DNA < LLOQ) is persisting 12-24 weeks after removal of therapy in 12 of 13 experimental patients achieving HBsAg < 1 IU/mL (REP 2139: 8/10, REP 2165: 5/10). Control of HBV infection is stable in the 13th (REP 2139) patient (HBsAg 1.91 IU/mL, HBV DNA 93 IU/mL) at 24 weeks follow-up. Serum ALT/AST has normalized in all these patients. Rebound of infection has occurred in all other experimental patients during follow-up, however clinical benefit (reversal of HBV DNA rebound and normal ALT/AST) is apparent in two additional patients.
Conclusion: REP 2139-based combination therapy is well tolerated and elicits the establishment of functional control of HBV infection persisting after removal of therapy (functional remission) in 80% of patients.

O-HBV-32

Greater prevalence of disease severity and associated co-morbidities with increasing age: a cross-sectional analysis of chronic hepatitis B patients in Saudi Arabia

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Background: Limited evidence is available on the age, prevalence of comorbidities and treatment pattern in patients with chronic hepatitis B (CHB) in Saudi Arabia. Our aim was to compare and characterize CHB patients in 2015 with CHB patients in 2010 and 2012.
Method: We conducted and compared three cross-sectional analyses of CHB patients $\geq$ 18 years of age with CHB defined as either positive HBsAg or a documented history of CHB in 2010, 2012 and 2015. Cross-sectional data was accessed from the multicentre Systematic Observatory Liver Disease (SOLID) registry provided by the Liver Disease Research Center of the King Saud University Medical City to retrieve eligible patients.
Result: We identified a total of 765 CHB patients registered in SOLID during different time-points: 274, 256 and 235 in 2010, 2012 and 2015, respectively. The median age was significantly higher in 2015 (47 years) compared to 2010 and 2012 (41 and 42 years, respectively; $p < 0.001$). The proportion of patients between 2010 and 2015 with hepatocellular carcinoma (HCC; range 1%–12%) and cirrhosis (range 5%–23%) were consistently higher in 2015 compared to 2010 and 2012 ($p < 0.0001$; cf. Figure 1). Additionally, more patients had coronary artery disease in 2015 compared with 2010 (10% vs. 4%; $p = 0.006$); or hyperbilirubinemia (18% vs. 9%;

Conclusion: As in Turkish society, lamivudine resistance may be seen in naive chronic hepatitis B patients in some societies. We, therefore, recommend taking this into account when choosing drugs with high genetic resistance barrier.

O-HBV-35

Inarigivir: a novel RIG-I agonist for chronic hepatitis B

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Background: Inarigivir (previously SB 9200) is an oral HBV antiviral with both direct acting activity and immune-modulation through activation of the pattern recognition receptor retinoic acid-inducible gene 1 (RIG-1). Inarigivir is currently being evaluated in the ACHIEVE trial, double-blind placebo controlled phase II studies of ascending doses of Inarigivir daily monotherapy or placebo (PL) for 12 weeks, followed by a switch to 300 mg Tenofovir (TDF) daily for a further 12 weeks. Here, we report the virological and serological responses of the 1st cohort inarigivir 25 mg and effects after switching to TDF.
Method: 20 treatment *naïve* non-cirrhotic HBV patients were randomised 4:1 to 25 mg SB 9200 or placebo. There were M: 12; 1F: 8, mean age 40 yrs, 18 Asian, 16 genotype B/C and 4 A /D with 11 HBeAg +ve and 9 HBeAg−ve.
Result: There were no clinical, haematological or biochemical SAEs and no interferon-like side effects. During Inarigivir therapy, 3/7 of the HBeAg−ve and 1/9 of the HBeAg+ve had greater than 1.0 log10 IU/ml reduction in HBV DNA (mean 0.6 log10, $p = 0.01$ vs placebo). 3 of 7 HBeAg−ve, and 2/9 HBeAg+ve subjects demonstrated > 0.5 log10 IU/ml decline in serum HBsAg. The serum HBV RNA fell by > 0.5 log10 copies/ml by week 12 in 10/16 patients; seven were HBeAg−ve, with 5 having > 3.0 log10 copies/ml to undetectable whilst 2 had a > 1.0 log10 copies/ml decline. In the 3 HBeAg + ve patients, 1 had a > 1.0 log10 copies/ml and 2 had > 0.5 log10 copies/ml decline in their serum HBV RNA. Hepatitis B core related antigen (HBcrAg) testing to week 12 revealed a similar antiviral response to the HBV RNA profiles, especially in the HBeAg−ve group. From 12-24 weeks TDF induced potent suppression of serum HBV DNA of > 3.0 log IU/ml decline or to undetectability. In Inarigivir/TDF group 6/16 (38%) patients achieved a HBsAg response of > 0.5 log IU/ml from week 12-24 which was more enhanced in HBeAg+ve patients and 4 of 9 of HBeAg+ve also achieved > 0.75 log decline in qHBeAg. Neither HBV RNA or HBcrAg responses were enhanced following the TDF switch. Patients with > 0.5 log IU/ml drop in HBsAg also demonstrated HBsAg epitope changes associated with a clearance profile, whilst anti-HBs complexed to HBsAg was observed to develop in 56% of inarigivir treated patients, possibly reflecting the emergence of an endogenous immune response.
Conclusion: Inarigivir at low dose 25 mg daily, demonstrated safety and significant antiviral effects on HBV replication, presumably at the level of viral RNA packaging, translation and reverse transcription with early suggestion of an immune mediated clearance response more apparent in HBeAg-ve patients.

O-HBV-36

Increasing age and comorbidities in 43,316 adult patients with chronic hepatitis B (CHB) from 2011 to 2016 in Japan: results of a real-world analysis

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Background: CHB affects approximately 1% of the general population in Japan with higher prevalence in older people. The aim of this study was to characterize the evolving CHB patient demographics including non-liver comorbidity burden in Japan as well as their changes over the recent 5 years (2011-2016).
Method: We used the Medical Data Vision (MDV) claims database to identify patients ≥ 18 years with ≥ 1 inpatient or 2 outpatient ICD-10 codes for CHB (B18.1) and with continuous enrollment for 6 months prior and post index date (first date of CHB diagnosis) during 1/1/2011–12/31/2016. Patient demographic and comorbidity data was reported from 2011 to 2016. The proportions of patients with comorbidities for each year was calculated for all CHB patients still observed in the database for that given year.
Result: A total of 43,316 patients met the study inclusion and exclusion criteria during the 2011 to 2016 period. Males made up 57.2% of the patients in 2011 and decreased to 54.6% in 2016 ($p < 0.0001$). The average age of patients was 61.3 ± 13.1 years in 2011 and increased to 64.2 ± 13.2 years in 2016 ($p < 0.0001$). The proportion of the population over 65 increased from 43.1% in 2011 to 66.0% in 2016 ($p < 0.0001$). Similarly, the proportion of patients over 75 years of age increased from 15.3% in 2011 to 21.6% in 2016 ($p < 0.0001$). The proportion of patients receiving antiviral therapy for HBV was fairly stable, at 32.8% in 2011 and 31.4% in 2016 ($p = 0.018$). The Charlson comorbidity index, an overall measure of patient comorbidity (covering 17 conditions), increased from 2.69 to 3.2 ($p < 0.0001$) with selected comorbidities summarized in Table 1. In 2016, 21.8% of CHB patients in Japan had cardiovascular disease (CVD), 36.7% with hypertension (HTN), 11.8% with diabetes (DM), 18.2% with renal impairment (RI), 4.0% with chronic kidney disease (CKD), 8.6% with osteoporosis/osteoarthritis/vitamin D deficiency, 4.5% with fragility (non-traumatic/non-pathological) bone fractures; all of which have increased significantly from 2011 ($p < 0.001$ to 0.029).
Among CHB patients 65 years or older observed in 2016, almost one-third (29.7%) had CVD, one-half (47.1%) with HTN, 14.7% DM, 5.4% CKD, 11.4% metabolic bone disease and 6.2% non-traumatic/non-pathological factures. As expected, even more patients 75 or older had comorbidity with over half (54.1%) having HTN, one-quarter with RI (24.3%) including 7.2% with CKD and close to 1 in 10 with fragility bone fracture.
Conclusion: Between 2011 and 2016, the Japanese CHB population has aged ($\sim$ 2 in $3 \geq 65$) and are having more comorbidities, which may affect CHB management and should be considered in their treatment and monitoring.

O-HBV-41

Screening of significant liver fibrosis in general populations and high risk HBV carriers in China

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Background: CHI3L1 is a new marker that have been recently demonstrated to be an excellent non-invasive marker for liver fibrosis caused by various factors including HBV, HCV, alcoholic and fatty liver diseases. In this study, we screened for significant liver fibrosis (SLF) in general populations and high risk HBV carriers in China in order to estimate prevalence of ALF in general population and in high-risk populations.
Method: Serum samples from 458 healthy individuals (median age 37 years old. 52.7% female and 47.3% male)from annual physical check-up population were analyzed for CHI3L1 using the ELISA kit from Hangzhou Proprium Biotech Co. Ltd., which has obtained Chinese FDA approval and CE mark permit. In addition, 217 HBV carriers with detectible HBsAg levels were enrolled and their serum samples analyzed for CHI3L1 levels.
Result: We used the concentration of CHI3L1 > 69.5 ng/ml (median of biopsy-confirmed S2 liver fibrosis) for significant fibrosis (Huang et al. OMICS, a Journal of Integrative Biology 19(6): 339-345, 2015). 44 of the 458 healthy individuals (9.61%) have CHI3L1 levels > 69.5 ng/ml (Table 1).The prevalence of significant liver fibrosis is 9.61%, which is greater than 6-7% which was reported for the prevalence rate of liver fibrosis in the adult population without known liver disease in Europe. In Europe, the cause of liver fibrosis is mostly associated with non-alcoholic fatty liver disease, however, in China, they are probably mostly associated with HBV carrier status as the prevalence of HBV carrier is about 8.4% based on the National Disease Supervision Information Management System of China between 2005 and 2010. (Yan et al. J Clin Transl Hepatol. 2014 Mar; 2(1): 15–22). We next focused on the analysis of significant liver fibrosis for HBV carriers in China. We found that 72 of 217 HBV carriers (33.18%) have CHI3L1 levels > 69.5 ng/ml (Table 1). High prevalence of liver fibrosis has been reported in other high risk populations. For example, Kwok et al. (Gut 2016; 65: 1359-68) reported a prevalence of 18% for diabetic populations and Harman et al. (BMJ Open 2015; 5: e007516.) reported 27% in NFALD and alcoholic liver disease populations.
Conclusion: The prevalence of significant liver fibrosis is 9.61% in the general populations and as high as 33.2% in HBV carriers in China. General screening of the general populations, and in particular, in the high risk HBV carriers in China, is warranted to reduce the burden of liver disease in the future.

Table 1. Percentage of individuals with advanced liver fiboris

Categories	Routine-check-up population	Total	Percentage
CHI3L1 > 69.5	44	458	9.61
	HBV carriers	Total	percentage
CHI3L1 > 69.5	72	217	33.18

O-HBV-42

The predictors analysis of early cirrhosis for chronic HBV carriers

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Background: Guidelines for the prevention and treatment of chronic hepatitis B in China for chronic HBV carriers are not recommended, but for chronic HBV carriers aged over 40 years were recommended to do a liver biopsy to identify the liver inflammation and fibrosis level. But limiting the invasive of the liver-biopsy most patients is difficult to accept, this study aimed at explore noninvasive warning systems of early cirrhosis for chronic HBV carriers over 40 years.
Method: 442 chronic HBV carriers over 40 years old (including 40 years) in Hepatobiliary Hospital in Jilin province form August 2012 to August 2015 accepted liver puncture biopsy, 89 cases (liver cirrhosis group) were diagnosed with cirrhosis according to Liver biopsy, 194 cases (control group) were diagnosed with fibrosis below the G2S2 stages (including G2S2). Using statistical software SPSS17.0, statistical analysis on correlation of liver biopsy results with liver function, peripheral blood cell counts, HBV DNA, HBsAg quantitative and Fibroscan.
Result: The cirrhosis group's age, history of hepatitis b, BMI and the proportion of drinkers were 53.3 ± 8.7 (years old)?42.7 ± 7.2 (years)?29.6 ± 3.9?65.17%, the corresponding indicators in control group were 44.6 ± 3.1?23.6 ± 5.8?21.8 ± 3.1?30.41%.
Conclusion: For chronic HBV carriers over 40 years, age, history of hepatitis b infection, obesity, alcohol intake, PLT < 110 × 109/l, and NEUT < 2.0 × 109/l were risk factors for liver cirrhosis. Fibroscan showed good coherence with liver cirrhosis

Session: Hepatitis C Virus Infection. Charpersons: Necati Ormeci; G N Yatoo; Harshad Devarbhavi

O-HCV-25

Patient characteristics and medication burden of chronic hepatitis C (CHC) patients in Japan from a Nationwide Real World Hospital Claims Database

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Background: Japan has the highest prevalence of Hepatitis C virus (HCV) infections in the industrialized world with approximately 1.5 million current infections. In addition, Japanese patients with HCV are elderly and thus may possess more comorbidities and higher pill burden. This study describes the pill burden and comorbidities in Japanese HCV patients in the Medical Data Vision (MDV) claims database.
Method: This was a retrospective cohort study of adult (≥ 18 years old) patients with chronic hepatitis C (CHC, ICD-10 code: B18.2) included in the MDV hospital claims database. The database contains information from inpatient and outpatient visits at 287 hospitals in Japan from Apr 2008–June 2016.
Result: Age and gender were derived based on direct reporting from the database, for the most recent CHC visit. Comorbidity prevalence was assessed using ICD-10 codes, based on a predefined list of comorbidities common to CHC patients. Patients who had received all oral direct acting antiviral (DAA) therapy were identified through receipt code for a prescription for a DAA. The average number of tablets ('pill burden') taken by DAA-treated patients was calculated for the 90 days prior/post first prescription date of a DAA. The study population included 173,796 patients (mean ± SD age 69 ± 14, 51.7% male), with a large proportion being over the age of 75 (40.7%). Highly prevalent comorbidities included hypertension

HBV-C2

Risk prediction model for hepatocellular carcinoma in treatment-naïve, non-cirrhotic chronic hepatitis B patients without alanine aminotransferase elevation

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Background: Precise prediction of hepatocellular carcinoma (HCC) risk is crucial in making decisions on antiviral treatment and surveillance in chronic hepatitis B (CHB). This study aimed to develop and validate a HCC risk prediction model for the CHB patients who are not traditionally subject to antiviral treatment due to no significant elevation of alanine aminotransferase (ALT) levels.
Method: The study subjects were recruited from a historical cohort of 5495 treatment-naïve, non-cirrhotic CHB patients with serum ALT levels <2' upper limit of normal (females, <19 IU/mL; males, <30 IU/mL) at a tertiary referral hospital in Korea. The patients were randomly assigned to either the development cohort or the validation cohort in 4:1 ratio. Cox proportional hazards regression model was used to predict HCC risks.
Result: During the total follow-up of 29,538 person-years, 221 patients (5.1%) in the development cohort and 45 (4.1%) in the validation cohort developed HCC. Old age, male gender, and lower platelet counts were found to be independently associated with an increased risk of HCC. Regarding HBeAg status and HBV DNA levels, HBeAg-positive patients with HBV DNA level <6 log10 IU/mL (hazard ratio, 6.89, 95% confidence interval [CI], 4.20–11.29) showed the highest risk. Based on these predictors, a 29-point risk model was developed, with HCC risk ranging from 0.01% to 42.0% at 3 years, 0.03% to 73.12% at 5 years, and 0.08% to 96.75% at 10 years. In the validation cohort, the area under receiver operating curves were 0.69 (95% CI, 0.55–0.85) at 3 years, 0.74 (95% CI, 0.63–0.83) at 5 years, and 0.83 (95% CI, 0.77–0.88) at 10 years.
Conclusion: A HCC risk prediction model was developed and validated based on the non-cirrhotic CHB patients with normal or mildly elevated ALT levels. The model could help assess the HCC risk among patients who are not subject to antiviral treatment which consequently call attention to the necessity of developing a new treatment guideline.

HBV-C3

Economic gains related to hepatocellular carcinoma (HCC) and decompensated cirrhosis (DCC) reduction in Japan is expected from treatment of chronic hepatitis C (CHC)

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Background: Japanese CHC patients are infected for a longer period of time, and at risk for HCC, an important complication of CHC. Highly effective Oral Direct Acting Antiviral (DAA) regimens for CHC can lead to high SVR rates which can reduce CHC complications and costs. This study used a decision analytic Markov model to estimate the economic benefit of HCV cure by reducing HCC and DCC in Japan.
Method: A hypothetical cohort of 10,000 HCV GT1b Japanese patients with a mean age of 70 was modeled with a hybrid decision tree and Markov state-transition model capturing the natural history of HCV infection over a lifetime horizon.
Result: It was assumed that 15% of the cohort had cirrhosis and 20% were treatment-experienced. Treatment options were assumed to be approved all-oral DAAs vs. no treatment (NT). Treatment efficacy was based on randomized controlled trials of DAA regimens. Transition rates and costs were obtained from Japan-specific data. The number of cases of DCC, HCC and quality-adjusted life years (QALYs) were projected for patients treated with an all oral DAA vs. NT. QALYs were monetized using a willingness to pay (WTP) threshold which varied from ¥4 to ¥6 million. The incremental savings associated with treatment were calculated by adding the projected cost of complications avoided to the monetized gains in QALYs.
The model showed that DAA treatment can avoid 1583 cases of HCC and 1162 cases of DCC, saving ¥618,076 and ¥251,329 per treated patient; respectively. If we combine both DCC and HCC as serious complications of HCV-cirrhosis in Japan, treatment leads to avoidance of 2745 cases of complications and the associated savings of ¥869,405 per treated patient. Additionally, DAA treatment can lead to an additional 1.59 QALYs gained per patient treated. The indirect economic gains associated with treatment-related QALY improvements were estimated to be ¥6,360,000, ¥7,950,000 and ¥9,540,000 per patient at WTP thresholds of ¥4 million, ¥5 million and ¥6 million. Total economic savings of HCV GT1 treatment with DAAs (vs. NT) was ¥7,229,405, ¥8,819,405 and ¥10,409,405 at these different WTP thresholds.
Conclusion: Treatment of HCV GT1b with all Oral DAAs in Japan can lead to significant savings related to avoidance of HCC and DCC.

HBV-C4

Early hepatitis B surface antigen seroclearance after commencement of antiviral treatment in patients with de novo HBV reactivation

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Background: Hepatitis B virus (HBV) reactivation can occur not only in chronic hepatitis B (CHB) patients, but even in patients with resolved infection, especially in those who had undergone hematopoietic stem cell transplantation (HSCT) or rituximab treatment. We evaluated the virologic-serologic responses after commencement of antiviral treatment in patients with de novo HBV reactivation.
Method: We reviewed 1,101 consecutive patients treated with rituximab or HSCT who had tested for HBV serum markers at a tertiary center from January 2006 to August 2014. Among them, a total of 341 HBsAg-negative/anti-HBc-positive patients who were followed up with HBV markers were included in the study. Clinical outcomes of the patients with de novo HBV reactivation were then compared with 34 CHB patients who started antiviral therapy during rituximab-based therapy or HSCT for hematological diseases.
Result: Forty-three out of the 341 patients (12.6%) experienced de novo HBV reactivation at median 25.1 months and the cumulative rates were 5%, 13%, and 26% at 1, 2 and 4 years, respectively. The median value of HBV DNA at reactivation was 6.2X106 IU/mL.

therapy(r=0.2675, P=0.0024). To exam the early genomics change in the peginterferon therapy, we used RNA-seq to detect HBeAg positive patients with the treatment of peginterferon which includes 4 patients with treatment response and 6 with no response. We found 217 different expressed genes by comparing the response and no response groups. Go analysis showed that the response of peginterferon therapy was related with innate immunity and type 1 interferon signal pathway, etc.

Conclusion: The different expressed biomarkers were found during interferon therapy, which may provide clues for the further understanding of interferon therapy.

HBV-C14

Assessment of treatment response by transient elastography during the tenofovir in nucleos(t)ide-naïve patients with chronic hepatitis B

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Background: Several longitudinal studies have demonstrated that elastography could be a useful tool for monitoring of liver fibrosis during the treatment of chronic hepatitis B. However, not enough studies assessing regression of liver fibrosis by elastography are available to date. Therefore, the purpose of this study was to evaluate the liver stiffness before and during the treatment and assess the usefulness of this non-invasive modality.

Method: 127 treatment-naïve patients started treatment with tenofovir. Liver stiffness measurement by a transient elastography was performed at baseline, after 6, 12, 18, and 24 months. The difference of results between baseline and each months of elastography were compared respectively by paired t-test methods.

Result: 115, 104, 75 and 54 patients had performed elastography at 6, 12, 18, and 24 months after tenofovir medication. Median liver stiffness values were decreased from 6.79 kPa (95% CI, 6.03 - 7.56) at baseline to 5.61 (95% CI, 4.93 – 6.28) 5.44 (95% CI, 4.75 – 6.12), 5.20 (95% CI, 4.36 – 6.05) and 5.15 (95% CI, 4.08 – 6.21) kPa to 6, 12, 18, 24, and 30 months after tenofovir medication. Liver stiffness was significantly decreased at 6 months (P = 0.007), 12 months (P = 0.001) 18 months (P = 0.015) compared with that of pretreatment

Conclusion: Liver stiffness was significantly improved in chronic hepatitis B patients with tenofovir treatment during 24 months. Considering the liver biopsy is invasive, costly, and associated with possible complications, transient elastography is useful to assess the progression or regression of liver fibrosis safely and serially.

HBV-C15

Projection of health outcomes using tenofovir alafenamide (TAF) for the management of chronic hepatitis B (CHB) in Japan

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Background: An estimated 1.2 million people in Japan have CHB. Current Japan Society of Hepatology guidelines recommend TAF, tenofovir disoproxil fumarate (TDF) and entecavir (ETV) as first-line treatment options. The 2017 EASL guidelines recommend that CHB patients with declining renal function/osteoporosis should be considered for switch to ETV or TAF with TAF preferred in lamivudine experienced patients.

Method: We estimated the health outcomes of a Japanese CHB population comparing TAF to ETV or TDF in 1,000 patients over a lifetime. Our model was developed using the Discretely Integrated Condition-Event (DICE) Simulation framework, which conceptualizes the disease and its management in terms of patients' conditions and events impacting these conditions. Model inputs were drawn from published RCTs, peer-reviewed Japanese literature, and real-world database analyses.

Result: Based on results of two pivotal registration trials, the model applied similar hepatitis B virus (HBV) suppression and resistance rates between TAF and TDF, but improved ALT normalization and bone/renal safety. Efficacy and safety data for ETV were obtained from published studies. From published literature, the model assumed that 20% of TE patients were lamivudine exposed and thus had higher viral resistance rates to ETV. Two treatment modalities were modeled: (1) 1st line treatment-naïve (TN) monotherapy and (2) TN and TE sequential therapy wherein treatments could be switched based on viremia and resistance.

Over a lifetime, TN patients initiated on TAF experienced better liver outcomes in terms of fewer compensated cirrhosis (CC), decompensated cirrhosis (DC), and hepatocellular carcinoma (HCC) events compared to ETV (Table 1). In terms of safety, patients that started on TAF had fewer chronic kidney disease stage 3 (CKDIII, 26 to 30 less per 1000 patients) and similar or fewer bone fracture (3 more to 14 less per 1000 patients) events compared to both ETV and TDF. However, it was found that the slight increase in fractures in TAF compared to ETV were due to TAF patients living longer and being able to accrue more fractures. Those who started on TAF similarly experienced higher life years (LY's, +0.1 to 0.2) and quality-adjusted life years (QALYs, +0.1 to 0.2).

Under sequential therapy, treatment sequences starting on TAF therapy experienced less CC (5 to 27 fewer per 1000 patients) and HCC (9 to 22 fewer per 1000 patients) events and higher LY's (+0.1 to 0.2) and QALYs (+0.1 to 0.2) compared to ETV and TDF starts. Additionally, patients given TAF as 1st or 2nd line experienced less CKDIII (107 to 155 fewer per 1000 patients) events and fractures (7 to 20 fewer per 1000 patients) compared to other treatment sequences.

Conclusion: TAF is projected to have fewer hepatic complications, and renal events when compared to TDF and ETV over a lifetime, driven by its favorable efficacy, safety and resistance profile.

Table 1. Number of Events over Lifetime

Treatment Sequence	Viral Resistance	CC	DC	HCC	Fracture	CKD III	LY's (discounted)	QALYs (discounted)
Treatment-Naïve 1st Line Monotherapy								
TAF	51	189	51	113	303	95	16.8	11.2
TDF	51	188	50	112	317	125	16.7	11.1
ETV	120	205	58	133	300	121	16.6	11.0
Treatment-Naive and Treatment-Experienced Treatment Sequences								
TAF→ETV → ETV+TAF	51	178	40	105	345	185	16.4	11.0
ETV→TDF → ETV+TDF	259	205	48	127	349	340	16.2	10.8
ETV→TAF → ETV+TAF	234	196	44	117	342	298	16.3	10.8
TDF→ETV → ETV+TDF	97	183	38	114	362	292	16.3	10.9

CC – Compensated Cirrhosis; DC – Decompensated Cirrhosis; HCC – hepatocellular carcinoma; CKDIII – Chronic Kidney Disease Stage 3; LY – Life Years; QALY – Quality Adjusted Life Years; ETV - Entecavir; TAF - Tenofovir Alafenamide; TDF - Tenofovir Disoproxil Fumarate

antiviral therapy. HCV infection in patients with LCP was detected, on average, in 10-15 years after its manifestation. Replacement of C282Y and H63D in the HFE gene was found in half of patients with LCP. In patients with anomalous homozygous genotypes C282C and H63H, reliable signs of the syndrome of chronic iron overload were noted. The combination of extrahepatic manifestations was observed in 5 (7.5%) patients. Of these, AIT and diabetes mellitus - in 2, LCP and AIT - in 2 and in 1 patient LCP was combined with AIT and Sjogren's syndrome. In 12 patients with extrahepatic manifestations, including those with co-infections, 2 stages of liver fibrosis were detected with non-invasive evaluation.

Conclusion: Thus, the etiological role of HCV as a trigger factor for extrahepatic manifestations must be considered in a complex relationship with other risk factors and evaluated as one of the important components of a multifactorial pathogenetic mechanism.

HCV-13

Impact of direct antiviral agents on health-related quality of life in patients of chronic hepatitis C with chronic kidney disease

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Background: Patient-reported outcomes (PRO) provide important information related to patients' experience in chronic diseases. Chronic hepatitis C (CHC) patients with chronic kidney disease (CKD) represent challenging population to treat where the health-related quality of life (HRQoL) are affected from both CHC and CKD. This study assessed effect of directly acting antiviral agents (DAAs) on HRQoL in patients of CHC with CKD.

Method: This prospective study conducted at a public teaching tertiary care hospital included adult patients of CHC with CKD (GFR<60 ml/min/1.73 m^2) prescribed with DAAs after ethical approval. HRQoL was assessed using Short Form 12 Health Survey Questionnaire before and at end of treatment (ETR). Physical Composite Score (0-100), Mental Composite Score (0-100), and SF6D utility index (0-1) were calculated where 0 indicated the lowest, 50 or 0.5 normal and 100 or 1 the highest level of health.

Result: A total of 40 patients with positive HCV RNA with or without anti-HCV positive were screened and 30 patients were included in the study [Males=25 (83.3%), mean age 43.3±12.4 years]. Cirrhosis was present in 5(17%) patients and 19(63.3%) patients were treatment naive. Twenty three (76.7%) patients had genotype (GT) 1, 4(13.3%) had GT3, 2(6.7%) had GT4, and only one (3.3%) had GT2 (Table 1). Patients were divided into two groups including 13(43.3%) patients with GFR <30 ml/min/1.73 m^2 and 17(56.7%) with GFR >30 ml/min/1.73 m^2. Of 13 patients with GFR <30 ml/min/1.73 m^2, 11 patients were on hemodialysis (HD). All Patients with GFR <30 ml/min/1.73 m^2 were prescribed half dose of sofosbuvir (SOF) (200 mg) with daclatasvir (DCV) (60 mg) irrespective of HCV genotype. Patients having GFR >30 ml/min/1.73 m^2 were prescribed DAAs on the basis of their HCV GT [GT 2&3 prescribed SOF 400mg with DCV 60mg; GT 1&4 prescribed combination of SOF 400 mg with ledipasvir 90 mg]. (Table 2) HCV RNA was negative in 30 (100%) patients at ETR. Overall, there was significant improvement in PCS at ETR achieved with DAAs (42±1.97 vs. 50±1.34, p<0.05). Similarly, baseline MCS improved after administration of DAAs (43.7±1.36 vs. 47±1.43, p<0.05) at ETR. SF6D utility index also improved from baseline value 0.62±0.02 to 0.73±0.02 (p<0.05). Improvement in PCS (HD, 34.6±2.28 vs. 43.1±1.45, p<0.05; non-HD, 45.8±2.42 vs. 54.2±1.96, p<0.05) & SF6D (HD, 0.56±0.01 vs. 0.64±0.01, p<0.05; non-HD, 0.56±0.02 vs. 0.66±0.02, p<0.05) was seen in all patients irrespective whether they were on HD or not. According to GT, significant improvement in HRQoL after treatment with DAAs was observed in GT1(42±2.1 vs. 50±1.45, p<0.05). Cirrhotic patients had improvement in both PCS and MCS (PCS, 39.3±4.18 vs. 49.2±3.83, p<0.05; MCS, 40.5±4.63 vs. 48.2±3.36, p<0.05) whereas non-cirrhotic patients had improvement only in PCS.(42±2.23 vs. 50.6±1.45, p<0.05)

Conclusion: Patients with CHC with CKD have impaired HRQoL both in mental and physical aspects. Treatment with DAAs improves HRQoL in these patients.

Table 1: HRQoL before and after treatment with DAAs

Patients	No.	Enrolment PCS	ETR PCS	p-value	Enrolment MCS	ETR MCS	p- value	Enrolment SF6D	ETR SF6D	p-value
Global	30	42±1.96	50.4±1.34	**0.0001**	43.8±1.36	47.2±1.44	0.02	0.62±0.02	0.73±0.02	0.0001
Hemodialysis	10	34.6±2.28	43.1±1.45	**0.004**	40.2±1.58	44.3±1.95	0.067	0.56±0.01	0.64±0.01	0.001
GFR>30ml/min /1.73m²	17	45.8±2.42	54.2±1.96	**0.0001**	47.2±1.67	49±1.7	0.186	0.56±0.02	0.66±0.02	0.0001
Renal Transplanted	17	48.3±2.15	54.6±1.19	**0.006**	46.8±1.77	49±2.01	0.167	0.68±0.02	0.77±0.03	0.001
Cirrhotic	5	39.3±4.18	49.2±3.83	**0.0001**	40.5±4.63	48.2±3.36	0.038	0.61±0.05	0.76±0.07	0.026
Non Cirrhotic	25	42±2.23	50.6±1.45	**0.0001**	44.7±1.36	47.1±1.61	0.071	0.63±0.02	0.72±0.02	0.0001
HCV Genotype1	23	42±2.1	50±1.45	**0.0001**	45±1.52	49±1.54	**0.004**	0.63±0.02	0.73±0.02	0.0001
GT2	1	44.91	55.1	NA	49.02	43.1	NA	0.62±12.5	0.75±0.19	0.253
GT3	4	39±7.82	51±5.3	0.062	38.3±4	40.2±4.22	0.391	0.56±0.04	0.68±0.04	0.09
GT4	2	47±12.51	52.3±7.89	0.22	42.1±6.07	47±7.62	0.395	0.63	0.88	NA
Treatment Naive	19	39±2.49	48±1.6	**0.0001**	43±1.33	46±1.97	0.053	0.6±0.02	0.7±0.02	0.0001
Experienced	11	46.1±2.85	55.3±1.55	**0.013**	46.1±2.91	49.5±1.84	0.122	0.66±0.04	0.77±0.03	0.01

ETR-End of the treatment, GT-genotype, p-value<0.05 considered as significant

Table 2: Impact of different combinations of sofosbuvir on HRQoL

GFR (ml/min/ 1.73m²)	HCV Genotype	DAAs	No.	Enrolment PCS	ETR PCS	p-value	Enrolment MCS	ETR MCS	p-value	Enrolment SF6D	ETR SF6D	p-value
>30	1,4	SOF400mg +LDV90mg	12	47.2±3.1	54.3±1.5	**0.013**	47.3±2	49.3±2.16	0.197	0.69±0.03	0.79±0.04	**0.005**
<30	any	SOF200mg +DCV60mg	15	34±2	44.7±1.75	**0.001**	39.5±1.6	45.5±1.9	**0.016**	0.55±0.01	0.67±0.02	**0.001**
>30	2,3	SOF400mg +DCV60mg	3	52.1±7.18	57.5±2.42	0.23	36.4±7.14	41.9±6.68	**0.027**	0.65±0.01	0.66±0.001	0.250

ETR-End of the treatment, p-value<0.05 considered as significant

HCV-14

Patient-reported outcomes in chronic hepatitis C patients with or without extrahepatic manifestations (EHMs) in Japan

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Background: Almost two-thirds of patients with Hepatitis C (HCV) infection experience EHMs which have been shown to increase mortality and add to the impairment of Health Related Quality of Life (HRQoL) and costs of management. The objective of this study was

to estimate the burden of EHMs of HCV in Japan with respect to HRQoL and work productivity.
Method: Data from the Japan 2010-2016 National Health and Wellness Survey (NHWS) (N=175,000) which is a nationally representative patient-reported survey of adults were used. Respondents who self-reported a doctor diagnosis of at least one of the following conditions in addition to HCV are considered positive for EHMs: Type 2 diabetes, depression, arthritis, fibromyalgia, Sjögren's or kidney disease.
Result: Patients with EHMs (n=307) were compared to HCV patients without any of the above mentioned conditions (n=754). Groups were compared on HRQoL (assessed via the mental [MCS], physical component summary [PCS] scores, and health state utility score from the SF-36v2), work productivity and activity related impairment (assessed via the WPAI-GH instrument), in a bivariate analysis.
A total of N=1,061 respondents reported a diagnosis of HCV (49.1% were female; mean age = 60) of which 307 respondents had any of the following conditions: Type 2 diabetes, depression, arthritis, fibromyalgia, Sjögren's or kidney disease and were classified as "HCV with EHM group" (unadjusted mean age = 56.8; Charlson comorbidity index score (CCI) = 4. The rest of the 754 patients classified as control group ("HCV without EHM") were older (unadjusted mean age 61.3) and had a lower CCI score of 1.3.

Compared with controls, respondents with EHMs had significantly lower MCS (41.69 vs. 48.06; $p<0.001$), PCS (45.08 vs. 49.15; $p<0.001$), and health state utility (0.66 vs. 0.74; $p<0.001$). Respondents with EHMs also had significantly greater absenteeism (10.56 vs. 4.67; $p<0.001$), presenteeism (32.9 vs. 18.83; $p<0.001$), overall work impairment (36.87 vs. 21.32; $p<0.001$), and activity impairment (37.75 vs. 24.93; $p<0.001$).
Conclusion: HCV is a systemic disease and treating HCV is expected to improve clinical outcomes as well as patient quality of life and productivity resulting from improvement of HCV related EHMs.

HCV-15

Quality of life of young women of different constitutional groups with HCV infection.

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Background: To monitor the quality of life in young women with chronic hepatitis C (CHC) of various somatotypes.
Method: The study included data from 56 women aged 18 to 39 years, 36 of them were diagnosed with HCV in the replication phase with moderate activity, 20 women were healthy and included in the control group. The study was conducted in the department of infectious diseases 3 - clinic of the Tashkent Medical Academy. The diagnosis of CHC has been confirmed by the detection in the blood of RNA-HCV, anti-HCV IgM, anti-HCV. The degree of activity of the inflammatory process was determined by increasing ALT value by more than three norms. Quality of life (QoL) was assessed using a general questionnaire MOS SF-36.
Result: MOS SF-36 showed a significant reduction ($P<0.05$) of QoL in all scales in patients with CHC compared to healthy women. Especially sharp changes were observed on the part of the mental component in comparison with physical. Differences in quality of life were unreliable in the group with an indeterminate somatotype, where the indicator "viability" differed little in the study and control groups (65.7 and 70 points, respectively, $p> 0.05$). During the time of the study, we were unable to detect a significant difference in the quality of life (except for the RAF scale) in patients with CHC of various somatotypes.
Conclusion: In patients with chronic hepatitis C, significantly lower quality of life is observed compared with the control group. From the somatotype, changes in mental and physical health indicators in patients with CHC do not depend significantly.

HCV-16

Real-world effectiveness and cost per SVR of sofosbuvir/velpatasvir chronic hepatitis C treatment

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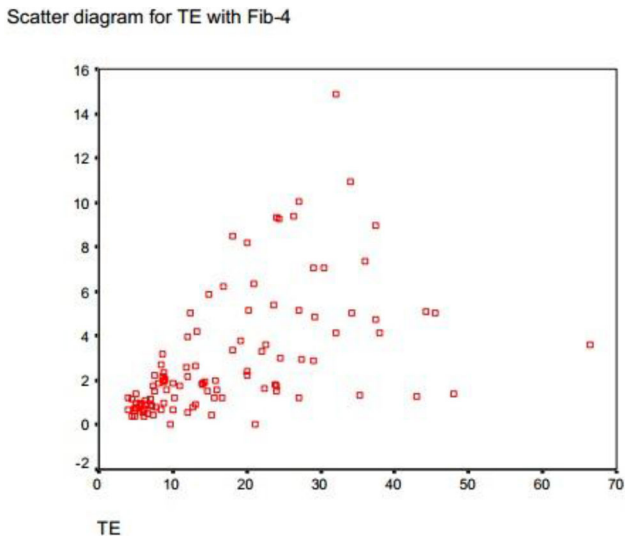
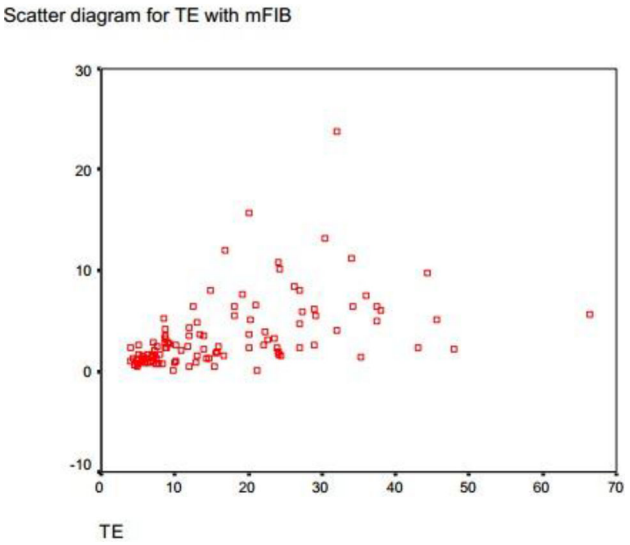
Background: Sofosbuvir/Velpatasvir (SOF/VEL) single tablet regimen (STR) is approved in Europe for the treatment of chronic hepatitis C (CHC) patients with genotypes (GT) 1-6 with the ASTRAL trials showing high sustained virological response (SVR). The aim of the present analysis is to characterize the population receiving SOF/VEL in clinical practice, describe outcomes and estimate the cost per SVR.
Method: This analysis included the first CHC patients treated with SOF/VEL in a single centre in Germany, and for whom sustained virological response after 12 weeks of follow-up (SVR12) will be available in October 2017. Baseline characteristics, prior treatment history, safety, effectiveness and cost per SVR were investigated. The analysis was performed using descriptive statistics.
Result: 126 patients received a 12w treatment and were included in the analysis. The mean (standard deviation -SD) age was 49.1 (10.8) years and 72% were males. Patient's GT distribution was 9%, 3%, 9%, 75%, 1%, 1% and 2% for GT1a, GT1b, GT2, GT3, GT4, GT5 and GT6, respectively. The METAVIR stage distribution of patients at baseline was 22%, 8%, 14%, 13% and 43% for F0, F1, F2, F3 and F4, respectively. 38 patients had RBV added to SOF/VEL (one patient was GT1a-F4, 3 were GT3-F3 and 34 were GT3-F4 with 6 who had decompensated disease) and one patient did not have RBV and had decompensated disease (GT1a-F4). Six patients were HIV co-infected and no patient was HBV co-infected. Overall, 84% of patients were treatment-naïve. Among the treatment experienced patients (n=20), 75% (n=15) had relapses or null responses to prior therapies. At baseline, co-morbidities were reported in 95% of patients, with arterial hypertension (15%) and depression (13%) being most common. The per protocol analysis for patients with available data (50/122) shows that 98% (49/50) achieved SVR12 (100% in GT3 patients (36/36)). Six adverse events (AEs) occurred; 3 were unrelated to treatment; 2 led to discontinuation and were possibly related to treatment and 1 was moderate and possibly related to treatment. Four patients discontinued the treatment; 2 due to lack of adherence; 1 was lost to follow-up and 1 because of AEs.
Conclusion: Early experience indicates that SOF/VEL is being used across all genotypes with majority use in GT3 population. Observed SVR rates are consistent with rates from pivotal trials.





HCV-27

Multiple comorbidities and significant pill burden in hepatitis C patients in a large US insured population

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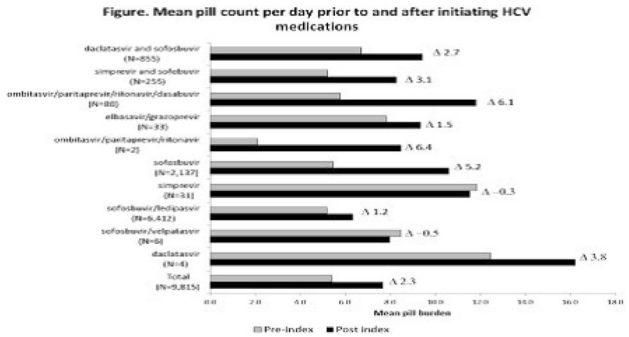
Background: Decreasing pill burden and regimen complexity have been associated with improved adherence and clinical outcomes in other diseases and this may extend to hepatitis C virus (HCV). This study describes the pill burden and comorbidities in patients treated for HCV.
Method: Commercial and Medicare Advantage insurance claims were used to identify patients who filled HCV medications between 11/1/2013 and 7/31/2016 (index date =first fill date of HCV medication). Patients were continuously enrolled in the health plan for 9 months prior and 6 months after index date. Pill burden was calculated as mean ±SD daily pill count for chronic, oral medications in the 90 days prior to (pre-HCV) and after index date (post-HCV).
Result: Descriptive statistics were used to compare patient demographics and pill burden changes by HCV medication. The study population included 9,815 patients (mean ±SD age 59.1±9.7, 63% male, 56% commercial). Highly prevalent comorbidities included pain (61%) and hypertension (50%). Pre- and post-HCV pill burden was 5.4 ±9.3 and 7.7 ±9.6, respectively. Pill burden was significantly higher among older patients and in those with more comorbidities ($p<0.001$). A greater proportion of Medicare patients had a post-HCV pill burden of ≥8 pills/day than in commercial (52% vs. 29%, $p<0.0001$). Post-HCV pill burden was higher among patients treated with more complex regimens, such as ombitasvir/paritaprevir/ritonavir ± dasabuvir (Figure; $p<0.001$). As such, patients with HCV have a substantial pill burden even prior to their initiation of HCV treatment, and more complex HCV regimens further increase the burden by up to 300%.
Conclusion: The majority of Japanese CHC patients are elderly with several comorbidities and high pill burden pre-DAA treatment. Patient pill burden may be an important consideration for HCV regimen selection.



HCV-28

Safety and efficacy of paritaprevir/r and ombitasvir combination therapy for HCV infected patients with Cryoglobulinemia

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Background: Cryoglobulinemia was reported to be observed in nearly 40% of hepatitis C virus (HCV) infected Japanese patients. So far safety and efficacy of interferon-free direct-acting antiviral agents (DAAs) for such patients has not been well assessed in Japan. In this study, we aimed to evaluate the safety and efficacy of HCV protease inhibitor (paritaprevir) and NS5A inhibitor (ombitasvir) combination therapy for genotype 1b infected patients with cryoglobulinemia.
Method: In this prospective multicenter study, genotype 1b HCV infected Japanese patients, including liver cirrhosis, with an immune disorder, cryoglobulinemia, treated with paritaprevir/r and ombitasvir combination therapy between February 2016 and September 2017 were included. We evaluated the sustained virologic response 12-weeks (SVR12), safety, and changes of cryoglobulinemia during and after the treatment.
Result: Eleven patients with cryoglobulinemia were treated with paritaprevir/r and ombitasvir combination therapy. The patients were aged 34–81 years (median, 63 years), and 63.6% (7/11) were male. One patient had NS5A RAV in L31M and one had NS5A RAV in Y93H at baseline. Of the 11 patients treated, 9 have reached SVR12. SVR12 data for all patients will be presented. Overall 100% (9/9) of