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HIGH CONCORDANCE OF SVR4, SVR12, AND SVR24 IN PATIENTS WITH HCV INFECTION WHO HAVE RECEIVED TREATMENT WITH SOFOSBUVIR

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Background and Aims: Sofosbuvir (SOF, formerly GS-7977), a potent uridine nucleotide analog now in Phase 3 development, has demonstrated >90% end-of-therapy (EOT) response and SVR12 in interferon-containing and interferon-free regimens, and across HCV genotypes. We evaluated concordance of SVR4 with SVR12 and SVR24 in the Phase 2 program.
Methods: Sofosbuvir has been explored in more than 500 patients, with and without ribavirin (RBV), or with peginterferon (PEG)+RBV in the phase 2 studies PROTON, ELECTRON, ATOMIC, and QUANTUM. In these studies, HCV RNA was measured at least at 4, 12, and 24 weeks following the end of treatment. We assessed the concordance of sustained virologic response (SVR) at these time points.
Results: 590 patients had HCV RNA measured at 4 and 12 weeks post-treatment, 538 at 4 and 24 weeks post-treatment, and 547 at both 12 and 24 weeks post-treatment. Relapse after having achieved SVR4 was uncommon; 8 patients who had achieved SVR4 subsequently relapsed by 12 weeks post-treatment and one patient who had achieved SVR12 relapsed at 24 weeks post-treatment. In two cases, patients with reported relapse at SVR4 were later found to have achieved SVR. Positive and negative predictive values are tabulated.

Table: Concordance of SVR4, SVR12, and SVR24

	PPV		NPV		Sensitivity		Specificity	
	SVR12	SVR24	SVR12	SVR24	SVR12	SVR24	SVR12	SVR24
SVR4	98.5	99.0	96.2	94.6	99.6	99.6	86.2	87.5
SVR12	–	99.8	–	97.5	–	99.8	–	97.5

PPV, positive predictive value; NPV, negative predictive value.

Conclusion: High levels of concordance between SVR4 and later time points were observed. There were few relapses in patients who achieved SVR4. Positive predictive values and sensitivity of SVR4 for SVR12 and SVR24 were >98.5%. Specificity and negative predictive values were lower, reflecting the relatively higher contribution of the few discordant patients in the much smaller number of patients who relapsed. SVR12 has a 99.8% positive predictive value, demonstrating the reliability of this time point for assessing a durable response.

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ALISPORIVIR INTERFERON-FREE TREATMENT ACHIEVED COMPARABLE EARLY HCV CLEARANCE RATES IN BOTH IL28CC AND IL28 CT/TT PATIENTS INFECTED WITH GENOTYPE 2/3 HCV

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Background: Host-targeting antiviral alisporivir (ALV) inhibits cyclophilin A that is essential for HCV replication. In the phase IIb VITAL-1 study involving treatment-naïve genotype (G)2/3 patients, early HCV clearance (<LLOQ, 25 IU/mL) was achieved in 42%-49% of patients after 4–6 weeks of ALV/RBV IFN-free treatment. Here we evaluate the impact of IL28B genotype on early viral clearance following IFN-free ALV therapy.
Methods: DNA samples were obtained from 169 (65% of all patients randomized to IFN-free ALV) patients who consented to pharmacogenetic assessment and received IFN-free ALV alone or ALV/ribavirin (RBV) treatment. IL28B genotype (rs12979860) was determined by Taqman SNP genotyping assay. Logistic regression was performed to evaluate association between IL28B genotype and HCV clearance with IFN-free ALV treatment at Weeks 4 and 6. The analysis was adjusted for race, baseline viral load, body weight, ALV exposure and treatment.
Results: Patients receiving IFN-free ALV treatment with IL28B CC genotype (rs12979860) had a higher rate of HCV clearance at week 4 or 6 compared with those with non-CC genotype: 36.26% vs 28.21% and 47.25% vs 32.05%, for Weeks 4 and 6 respectively, however the difference in RVR was not significant ($p = 0.12$ for Week 4; $p = 0.025$ for Week 6). Subgroup analysis with Caucasians only ($n = 95$) revealed significant association between IL28B genotype and response at Week 4 ($p = 0.041$) and week 6 ($p = 0.006$). No significant impact of IL28B genotype was observed in subgroup analysis with Asians only ($n = 70$). Additional analysis of the effect of ALV exposure on early HCV clearance with ALV/RBV demonstrated that, following ALV/RBV therapy, patients with low ALV exposure (Cmin <128 ng/mL), only 5% (1/20) of IL28B CT/TT (rs12979860) achieved RVR compared to 39% (7/18) for patients of CC genotype. In contrast, in patients with high ALV exposure (Cmin >423 ng/mL), those with IL28B CC and non-CC achieved the same rate of RVR (50%, 12/24, and 50%, 7/14 of non-CC and CC patients, respectively).
Conclusions: In treatment-naïve HCV G2/3 patients receiving Alisporivir+RBV, interferon-free treatment, high alisporivir exposure is more important than IL-28 genotype in determining early HCV clearance.

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EARLY VIROLOGIC RESPONSE (EVR) IN TREATMENT-NAÏVE MONO-INFECTED CHRONIC HEPATITIS C (CHC) PATIENTS TREATED WITH CEPEGINTERFERON-alfa-2b (cePEG-IFNα-2b) PLUS RIBAVIRIN

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Introduction: CePEG-IFNα-2b is a new pegylated form of interferon alfa (IFN-α) containing linear polyethylene glycol (PEG) (20 kDa). CePEG-IFNα-2b has a single isomer and characterized by a stable bond between PEG and IFN molecules. Pharmacokinetic profile of cePEG-IFNα-2b allows once weekly administration.
Methods: Multicenter open-label randomized phase II study to determine the efficacy and safety of cePEG-IFNα-2b compared with peginterferon-alfa-2b (PEG-IFNα-2b) in subjects with CHC. 150 treatment-naïve patients were randomized into 3 groups: cePEG-IFNα-2b 1.5 μg/kg/week, cePEG-IFNα-2b 2.0 μg/kg/week, and a reference group of PEG-IFNα-2b 1.5 μg/kg/week in combination with ribavirin.
Results: Comparative ITT-analysis showed absence of differences between groups in frequency of EVR. In cePEG-IFNα-2b groups (regardless of a dose – 1.5 or 2.0 μg/kg) EVR was observed in 94%, in PEG-IFNα-2b group – in 88% of patients. Complete EVR (HCV RNA ≤15 IU/mL) was recorded in 88% and 84% of patients receiving cePEG-IFNα-2b 1.5 and 2.0 μg/kg, respectively, in the reference group – in 84% of patients.