Welcome to the sixteenth issue of Hepatitis Research Review.

An analysis of phase III registration data for sofosbuvir, with or without interferon, reports a high degree of concordance between a sustained virological response (SVR) at 12 weeks post-treatment (SVR12) and SVR24 across hepatitis C virus (HCV) genotypes 1–6. The data did not support SVR4 as a valid efficacy endpoint. The study authors conclude that SVR12 is appropriate for determining “cure” rates in trials and in clinical practice.

An analysis of data from a phase I/II trial involving patients with undetectable hepatitis B virus (HBV) DNA who had been treated with nucleos(t)ide analogues for a median of 3 years demonstrates good tolerability of an HBV envelope-expressing DNA vaccine but no decrease in risk of relapse or in the rate of virological breakthrough. The study authors suggest in the light of their findings, other immunomodulatory strategies should be evaluated, including other vaccines (T cell vaccine), epitopes or modes of delivery.

I hope you enjoy the selection in this issue and I welcome your comments and feedback.

Kind Regards,
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Loss of hepatitis B surface antigen in a real-life clinical cohort of patients with chronic hepatitis B virus infection

Authors: Habersetzer F et al.

Summary: In this study, a real-life clinical cohort of 315 patients with chronic hepatitis B virus (HBV) infection was followed for a mean of almost 6 years to determine parameters associated with hepatitis B surface antigen (HBsAg) clearance. At study entry, 109 (34.6%) were inactive HBsAg carriers, 204 (64.8%) had chronic active hepatitis (CAH), and two (0.6%) were immune-tolerant carriers. During follow-up, 128 (62.7%) of the 204 patients with CAH received antiviral therapy. Sixty-nine had HBeAg-positive CAH: 55 (79.7%) were treated and 14 (20.3%) untreated. Of the 135 patients with HBeAg-negative CAH, 73 (54.1%) were treated and 62 (45.9%) untreated. The annual HBsAg clearance incidence rate amongst inactive carriers (23.4 cases per 1000 persons-years) was higher than that of CAH groups. The clearance incidence rates (in cases per 1000 persons-years) of CAH groups were: treated HBeAg-positive (20.7), untreated HBeAg-positive (19.1), treated HBeAg-negative (10.1), and untreated HBeAg-negative (8.1). The only predictors of HBsAg clearance were older age (p=0.001) and inactive carrier status (p=0.019).

Comment: This is the first reported study seeking to assess the incidence and determinants of HBsAg clearance in a cohort of 315 non-selected patients managed in a real-life clinical setting, taking into account the various phases of chronic HBV infection, as defined by international practice guidelines, and anti-HBV treatment. Overall, 9% cleared HBsAg after a mean follow-up of almost 6 years. Older age and an inactive phase of infection (durable normal serum ALT and low HBV DNA levels), but not antiviral therapy, were significantly associated with HBsAg clearance. The findings point to an important role for host-related immunological factors in achieving viral clearance, but require confirmation in larger studies that include patients of varying ethnic backgrounds.

Reference: Liver Int. 2015;35(1):130-9

Abstract
Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus

Authors: Yoshida EM et al.

Summary: For this study, data were retrospectively analysed from 5 phase III clinical trials of sofosbuvir-containing regimens, with or without interferon, involving a total of 863 patients infected with hepatitis C virus (HCV) genotypes 1–6. The study researchers systematically assessed the concordance between sustained virological response (SVR) – as defined by HCV RNA levels below a designated threshold of quantification – at 4 weeks post-treatment (SVR4) and SVR12, and between SVR12 and SVR24. Overall, 779 of 796 patients (98.0%) with an SVR4 also achieved an SVR12; the positive predictive value (PPV) of SVR4 for SVR12 was 98% and the negative predictive value (NPV) 100%. Of the 779 patients with an SVR12, 777 (99.7%) also achieved an SVR24, making the PPV of SVR12 for SVR24 >99% and the NPV 100%. Of patients who relapsed post-therapy, 77.6% did so within 4 weeks of completing therapy.

Comment: The authors report a post-hoc analysis of data obtained from phase III registration studies of sofosbuvir, a nucleotide analogue prodrug that targets the nonstructural protein 5B polymerase of HCV. The findings support SVR12 as an appropriate efficacy endpoint for sofosbuvir-ribavirin treatment, irrespective of whether or not it is combined with pegylated interferon. A high degree of concordance between SVR12 and SVR24 was apparent across HCV genotypes 1–6, extending observations in the previous SPARE trial, in which 100% concordance between SVR12 and SVR24 was evident in genotype 1 patients managed with sofosbuvir and ribavirin. Conversely, one-fifth of all patients who relapsed did so between post-treatment weeks 4 and 12, demonstrating that SVR4 is not a suitable efficacy endpoint.


Abstract

Clinical evidence and bioinformatics characterization of potential hepatitis C virus resistance pathways for sofosbuvir

Authors: Donaldson EF et al.

Summary: These researchers developed protocols to independently analyse genotypic resistance analyses based on next-generation sequencing of sofosbuvir data from 5 clinical trials. The study researchers also used structural bioinformatics approaches to characterise potential resistance-associated substitutions. Analyses revealed four low-frequency, treatment-emergent substitutions occurring at conserved NS5B amino acid positions in 2.2% to 4.4% of subjects who experienced virological failure across clinical trials: L159F (sometimes in combination with L320F or C316N) and V321A. In addition, baseline polymorphisms at position 316 were potentially associated with reduced response rates in HCV genotype 1b subjects. Analyses of these variants modelled in NS5B crystal structures indicated that all of these substitutions could feasibly affect sofosbuvir anti-HCV activity.

Comment: This report from the Division of Antiviral Products, U.S. Food and Drug Administration, independently analysed genotypic resistance data pertaining to sofosbuvir that was obtained in five clinical trials and based on next-generation sequencing. Sofosbuvir has a high barrier to resistance and of the 240 subjects who failed sofosbuvir therapy across the clinical trials analysed, the majority experienced virological relapse and had no demonstrable resistance-associated NS5B substitutions. However, the investigators found four low-frequency NS5B substitutions (L159F, V321A, C316N and S282R) potentially associated with failure of sofosbuvir-based therapy, adding to current knowledge concerning this important, emerging anti-HCV therapeutic agent.


Abstract
Serum hepatitis B virus RNA levels as an early predictor of hepatitis B envelope antigen seroconversion during treatment with polymerase inhibitors

**Authors:** Van Bimmerm F et al.

**Summary:** This study determined whether serum HBV RNA levels during polymerase inhibitor treatment might be helpful for predicting hepatitis B envelope antigen (HBeAg) seroconversion. Change in mean HBV RNA levels in serial serum samples from 62 patients with chronic HBV infection (50 HBeAg-positive) treated with antivirals for a mean 30 months. A new rapid amplification of complimentary DNA-ends-based real-time polymerase chain reaction was established for quantitative analysis of polymerase chain reaction products. Change in mean HBV RNA levels from baseline to month 3 was 0.32 log10 copies/mL, respectively, in HBeAg-positive and -negative patients with HBeAg seroconversion (p<0.001 for months 3 and 6). HBeAg-negative patients had a similar decline in HBV RNA levels. In comparison with levels of HBV DNA, HBeAg, alanine aminotransferase, and HBV genotype, age, and sex, the decline of HBV RNA levels at months 3 and 6 of treatment was a better predictor of HBeAg seroconversion.

**Reference:** Hepatology. 2015;61(1):66-76

Statin use is associated with a reduced risk of fibrosis progression in chronic hepatitis C

**Authors:** Simon TG et al.

**Summary:** This study analysed data from serial liver biopsies performed over a 3.5-year period in 543 patients with chronic HCV and advanced hepatic fibrosis participating in the Hepatitis C Antiviral Long- term Treatment Against Cirrhosis (HALT-C) Trial. None of the participants had cirrhosis at study entry. Fibrosis progression occurred in 3/29 (10%) statin users and 145/514 (29%) non-users. The unadjusted hazard ratio (HR) for fibrosis progression among statin users compared to non-users was 0.32 (95% CI, 0.10 to 0.99). This association remained significant after adjusting for established predictors of histological outcome, including body mass index, platelets and hepatic steatosis (adjusted HR 0.31; 95% CI, 0.10 to 0.97). Over the study period, the mean change in Ishak fibrosis score was -0.34 for statin users and -0.42 in non-users (p=0.006, after adjusting for baseline fibrosis score).

**Comment:** Studies performed in animal models have shown that statins, in addition to the activation of hepatic myofibroblasts and prevent both proliferation of hepatic stellate cells and their production of collagen. This study, the first to prospectively assess the effect of statins on hepatic fibrosis in humans, found that statin treatment was associated with a significant reduction in the rate of fibrosis progression in patients with advanced HCV infection. A relatively long duration of follow-up and availability of histological data obtained from serial liver biopsies represent strengths of the study. The number of statin-treated patients (n=29) was small in comparison to the number of non-statin-treated patients (n=514), and corroboration of the findings in larger cohorts of statin-treated patients are warranted.

**Reference:** J Hepatol. 2015;62(2):18-23

Telbivudine plus pegylated interferon alfa-2a in a randomized study in chronic hepatitis B is associated with an unexpected high rate of peripheral neuropathy

**Authors:** Marcellin P et al.

**Summary:** This open-label study randomised 159 treatment-naïve patients with HBeAg-positive chronic HBV to receive telbivudine in combination with PegIFNα-2a (n=50), telbivudine alone (n=55), or PegIFNα-2a alone (n=54). At week 24, antiviral efficacy and safety data were available for 18, 49 and 43 patients in each treatment group, respectively. The study was terminated early due to increased rates of peripheral neuropathy in the combination therapy group (7 patients vs 1 patient on telbivudine alone and none of the PegIFNα-2a monotherapy cohort). Peripheral neuropathy was not associated with other variables (e.g., pharmacokinetic data, treatment efficacy, ALT levels, creatine kinase elevations). At week 24, undetectable HBV DNA (<50 copies/mL) was achieved by 71% (12/17) of combination therapy recipients, 35% (7/20) of telbivudine monotherapy recipients and 7% (3/40) of PegIFNα-2a monotherapy recipients (p=0.022 for combination therapy vs PegIFNα-2a).

**Comment:** Since no currently available treatment modality is associated with high rates of HBeAg seroconversion and HBeAg clearance in patients with chronic HBV infection, interest has focussed on a possible role for combination therapies using antiviral agents having additive or synergistic effects. Telbivudine is a potent inhibitor of HBV replication. This study, performed in treatment-naïve patients with HBeAg-positive chronic HBV infection, aimed to determine whether combination telbivudine and PegIFN therapy resulted in superior antiviral efficacy and higher rates of HBeAg and HBsAg seroconversion than either drug alone. Despite significantly reduced HBV DNA levels at treatment week 24 in the combination therapy group, the study was terminated early due to an unexpectedly high rate of peripheral neuropathy, the mechanism of which is currently unknown. Combination telbivudine and PegIFN therapy should, therefore, not be used.

**Reference:** J Hepatol. 2015;62(2):41-7

Quantification of HBsAg in nucleos(t)ide-naive patients treated for chronic hepatitis B with entecavir or with or without tenofovir in the BE-LOW study

**Authors:** Zoulim F et al.

**Summary:** In the BE-LOW study, 379 nucleos(t)ide-naive patients with HBV-positive or -negative chronic HBV were randomised to receive entecavir 0.5 mg/day alone (n=162) or in combination with tenofovir 300 mg/day (n=197) for 100 weeks. The study researchers examined the association between changes in HBsAg levels (quantified at baseline and at weeks 12, 48, and 96) and response to treatment. At baseline, mean HBsAg levels were comparable across subgroups by ALT, genotype, age, and treatment type, but were higher in HBsAg-positive than in HBsAg-negative patients. At weeks 12, 48 and 96, mean HBsAg changes from baseline were more pronounced in HBsAg-negative than in HBsAg-positive patients, in patients with genotype A than in those with genotypes C or D, and in patients with elevated baseline ALT, but were similar in treatment groups and between patients of different age categories. Mean HBsAg changes over 96 weeks were comparable in patients with or without HBV DNA <50 IU/mL at week 96, but among patients that were HBsAg-positive at baseline, changes were greater for those with week 96 HBsAg loss than for those without.

**Comment:** This is the first study to investigate quantitative HBsAg kinetics in patients with chronic HBV infection treated with entecavir, alone or in combination with tenofovir. Greater mean changes in quantitative HBsAg values, when assessed up to week 96 of treatment, were apparent in patients with elevated ALT values at baseline, those infected with genotype A compared with genotypes C or D and HBsAg-negative compared to HBsAg-positive patients, in whom more pronounced quantitative HBsAg level declines were associated with a likelihood of HBsAg loss. Additional studies, including analyses with longer follow-up, will be required to determine if on-treatment quantitative HBsAg levels may also be predictive of HBsAg seroconversion.

**Reference:** J Hepatol. 2015;62(2):56-63
Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy

Authors: Huang H et al.

Summary: This study from China compared the efficacy of entecavir and lamivudine in preventing HBV reactivation in HBsAg-positive patients with untreated diffuse large B-cell lymphoma undergoing chemotherapy treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Patients received entecavir 0.5 mg/day (n=61) or lamivudine 100 mg/day (n=60), beginning 1 week before the initiation of R-CHOP treatment and continuing for 6 months after completion of chemotherapy. Rates of HBV-related hepatitis were significantly lower with entecavir compared with lamivudine (0% vs 13.3%; p=0.003), as were rates of HBV reactivation (6.6% vs 30%, respectively; p=0.001) and chemotherapy disruption (1.6% vs 18.3%, respectively; p=0.002). Treatment-related adverse events were reported for 15 patients (24.6%) in the entecavir group and 18 (30%) in the lamivudine group (p=0.50).

Comment: The authors report the first randomised clinical study comparing prophylactic entecavir and lamivudine to prevent HBV reactivation in HBsAg-positive patients treated with R-CHOP for lymphoma. Prophylactic entecavir therapy, commencing one week prior to R-CHOP and continuing until 6 months after R-CHOP completion, was found to be more effective than lamivudine, with significantly lower rates of HBV reactivation (6.6% vs 30.0%), HBV-associated hepatitis (0% vs 13.3%) and requirement for anti-lymphoma treatment disruption (1.6% vs 18.3%). In addition, nearly 40% of instances of HBV-related hepatitis that occurred despite lamivudine prophylaxis arose after the withdrawal of antiviral prophylaxis, suggesting that a 6-month period of cover following R-CHOP discontinuation is insufficient when lamivudine is used. By contrast, no cases of HBV-related hepatitis occurred within this time frame in patients treated with entecavir. The findings clearly support the use of entecavir rather than lamivudine in this patient group.

Reference: JAMA. 2014;312(23):2521-30

Abstract

Once-daily simprevir is now PBS listed

PBS Information: This product is listed on the PBS as a Section 100 item. Refer to PBS Schedule for full authority information.

Janssen-Cilag


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