Annals of Hepatology

CONCISE REVIEW

The Official Journal of the Mexican Association of Hepatology, the Latin-American Association for Study of the Liver and the Canadian Association for the Study of the Liver

Concordance of sustained virologic response at weeks 4, 12 and 24 post-treatment of hepatitis C in the era of new oral direct-acting antivirals: A concise review

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ABSTRACT

The goal of treatment for chronic hepatitis C viral (HCV) infection is to cure the infection rather than suppress the virus. Historically, a sustained virological response (SVR) defined as undetectable HCV RNA at 24 weeks following the completion of treatment was considered the gold standard to define successful eradication of the virus as a primary endpoint in clinical trials. SVR measured at 12 weeks post-treatment has been shown to be highly concordant with SVR24 in trials of pegylated interferon and ribavirin. The appropriateness and durability of SVR12 as the efficacy endpoint with new oral direct-acting antivirals is less established. A literature search was performed using PubMed, EMBASE and CENTRAL databases to identify any studies that examined the concordance between SVR24 and earlier time points. Two studies and 4 abstracts were found that performed concordance analyses using positive and negative predictive values. Overall, SVR4 and SVR12 were highly concordant with SVR24 with high positive (> 97%) and negative (> 94%) predictive values; however there was a higher risk of HCV relapse occurring after post-treatment week 4. The majority of the data focused on SVR12 and demonstrated that SVR12 reliably predicted SVR24 in several populations infected with HCV (treatment-naïve, prior null responders, different genotypes) using various new oral direct-acting antiviral regimens. In conclusion, the available data suggests that SVR12 is a reliable assessment of HCV eradication and could be used instead of SVR24 for drug development clinical trials assessing efficacy of new direct-acting antivirals. Data on the long-term durability of SVR12 is still needed.

Key words. Hepatitis C. Direct-acting antiviral. Sustained virologic response. Concordance. Predictive value.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a global health problem and affects more than 180 million people worldwide.[1] Approximately 500,000 people died from HCV-related liver disease in 2010.[2] HCV, a single-stranded RNA virus, lacks the ability to incorporate its genome into a form in which recurrent viremia can emerge. Therefore, the goal of treatment is to cure the infection rather than suppress the virus. Historically, a sustained virological response (SVR) defined as undetectable HCV RNA by a sensitive assay (polymerase chain assay) at 24 weeks following the completion of pegylated-interferon (peg-IFN) and ribavirin (RBV) treatment was considered the gold standard to define successful treatment of HCV infection in clinical trials and for regulatory approval of new HCV therapies.[3,4] As a surrogate endpoint, SVR24 is associated with a reduction in the risk of hepatocellular carcinoma, liver-related decompensation, liver-related mortality and all-cause mortality and is widely considered indicative of cure.[5,6] The cut-point of 24 weeks was somewhat arbitrary and based on observations in large cohorts treated for HCV that relapse, defined as reoccurrence of detectable HCV RNA following achievement of SVR24, occurred in less than 1% of patients.[6-8] Further studies have shown SVR measured at 12 weeks post-treatment is highly concordant with SVR24.[9-11] Given the high concordance of SVR12 and SVR24 with IFN monotherapy and peg-IFN/RBV and the desire to expedite clinical trials, the US Food and Drug Administration and European Medicines Agency accepted SVR12 as an endpoint for clinical trials evaluating HCV therapies as a result of SVR12 being highly

Manuscript received: September 16, 2015. **Manuscript accepted:** December 10, 2015.

DOI:10.5604/16652681.1193693

predictive of SVR24 and is incorporated into clinical guidelines.[12] In the advent of the new oral direct-acting antivirals (DAAs), the trend has been to use SVR12 as the primary efficacy endpoint in clinical trials. The new DAAS are much more effective than previous treatment with peg-IFN/RBV with or without a protease inhibitor (telaprevir or boceprevir) with HCV eradication rates of more than 90% in the majority of patients, depending on the HCV genotype and absence of cirrhosis.[13] Treatment durations are being shortened from the previous 24 to 48 weeks to 12 or 24 weeks and in some cases as short as 8 weeks as a result of faster viral eradication.[13] The potential benefits of earlier SVR determination include less PCR testing and facilitation of drug development and approval by improving clinical trial efficiency. For clinical trials assessing treatment durations of 8 to 12 weeks, waiting an additional 24 weeks to determine SVR may seem excessive. However, if SVR at earlier time points does not adequately predict SVR24 the risks would include a false sense of security and missing relapses. Since the original shift to SVR12 as a primary efficacy endpoint for regulatory approval clinical trials was based on data with peg-IFN and RBV, the appropriateness and durability of SVR12 as the efficacy endpoint with the new oral DAAs is less established. The aim of this article is to provide a review of the evidence supporting earlier determination of SVR including 4, 8, and 12 weeks post-treatment for HCV with new oral DAAs by presenting data from studies that have performed concordance analyses.

MATERIAL AND METHODS

A literature search was performed in August 2015 using PubMed, EMBASE, and CENTRAL databases for all clinical studies and conference abstracts that examined the concordance of SVR 12 and SVR 24. Search terms included hepatitis C, sustained virologic response, concordance, sensitivity and specificity, and predictive value. Articles were limited to the English language and were excluded if they did not include a new oral DAA (excluding telaprevir, boceprevir) as part of the treatment regimen. The following data was extracted: direct-acting antiviral regimen, number of patients and types of genotypes treated, SVR rates at post-treatment weeks 4,12 and 24, and reported positive and negative predictive values (PPV and NPV respectively). Study authors were contacted for missing data as required. In cases where predictive values were not reported or could not be obtained, they were calculated using the reported SVR data. Data was extracted from the intention-to-treat or per protocol analysis, as reported by the study authors. Concordance between SVR12 and SVR24 was the primary outcome of interest.

RESULTS

Two articles and 4 abstracts were retrieved that specifically examined the concordance between SVR4, SVR12 and SVR24 using SVR rates determined in clinical trials investigating new oral DAAs. Concordance was assessed using positive and negative predictive values. SVR was defined as undetectable HCV RNA levels with a lower limit of quantification of 25 IU/mL.

Poordad, *et al.* performed an analysis of SVR rates in a subpopulation of the AVIATOR trial.[14] AVIATOR was a randomized, open-label, multicenter phase 2b trial that examined the effectiveness of a DAA regimen consisting of paritaprevir plus ritonavir, ombitasavir and dasabuvir with or without RBV for 12 to 24 weeks.[15] The study included adults infected with HCV genotype 1 who were treatment-naïve or prior null responders to peg-IFN/RBV with no evidence of cirrhosis. Those with concomitant human immunodeficiency virus or hepatitis B virus infection were excluded. The objective of the analysis of Poordad, *et al.* was to assess the concordance of SVR at 4 weeks, 12 weeks and 24 weeks in the 247 subjects that were treated with paritaprevir plus ritonavir, ombitasavir and dasabuvir with RBV for 12 or 24 weeks. The SVR rates assessed by intention-to-treat analysis for weeks 4, 12, and 24 post-treatment exceeded 93% and are presented in table 1. The concordance of SVR4, SVR12 and SVR24 using positive and negative predictive values is shown in table 2. There were no relapses post-treatment week 4; the discordance between rates of virological response is a result of lost to follow-up in which the authors conservatively considered missing data as treatment failures.

Yoshida, *et al.* performed a retrospective concordance analysis of SVR rates in 5 phase III clinical trials (NEUTRINO, FISSION, POSITRON, FUSION, VALENCE) that assessed the efficacy of sofosbuvir-containing regimens in subjects with known virologic outcomes.[16] The sofosbuvir-containing regimens included sofosbuvir plus peg-IFN and RBV for 12 weeks in genotypes 1, 4 to 6, and sofosbuvir plus RBV for 12 and 24 weeks for genotype 2 and 3, respectively. Rates of SVR4, SVR12 and SVR24 by HCV genotype are presented in table 1. Overall, 85 of 863 patients experienced virological relapse. Of those subjects that relapsed, 77.6% relapsed within the first 4 weeks post-treatment, with 20% relapsing between weeks 4 and 12 post-treatment. Concordance of SVR rates is shown in table 2. Overall, 98% of subjects that achieved SVR4 also achieved SVR12. Similarly, 99.7% of subjects that achieved SVR12 achieved SVR24. The concordance analysis demonstrated that achieving SVR12 with sofosbuvir plus peg-IFN /RBV for 12 weeks for genotypes 1, 4 and 6 or sofosbuvir plus RBV for 12 weeks for genotype had 100% positive and negative predictive value. For genotype 3

Table 1. Rates of sustained virologic response (SVR) at 4, 12 and 24 weeks post-treatment.

Study	Patient population	Antiviral regimen	SVR4% (n/N)	SVR12% (n/N)	SVR24% (n/N)
Poordad, et al.[14]	n = 247 adults, HCV GT1 Treatment-naïve or prior null responders to PEG-IFN and RBV, no evidence of cirrhosis Excluded HIV or HBV co-infection	Paritaprevir/ritonavir, ombitasavir, dasabuvir + RBV x 12 or 24 weeks	96.4 (238/247)	95.5 (236/247)	93.6 (231/247)
Yoshida, et al.[16]	n = 863 adults HCV GT 1, 4-6: n=327; HCV GT 2:n=294; HCV GT 3: n = 250 Treatment-naïve or prior null responders to PEG-IFN and RBV Excluded HIV or HBV co-infection	GT1,4-6:sofosbuvir + peg-IFN/RBV for 12 weeks GT 2: sofosbuvir + RBV x 12 weeks GT 3: sofosbuvir + RBV x 24 weeks	GT 1, 4-6:92.4 (302/327) GT2: 94.2 (277/294) GT3: 87.2 (218/250)	GT1, 4-6: 90.5 (296/327) GT2: 91.8 (270/294) GT 3: 85.2 (213/250)	GT1, 4-6: 90.5 (296/327) GT2: 91.8 (270/294) GT3: 84.4 (211/250)
Bernstein, et al.[17]	n = 1,952 adults, HCV GT1 Treatment-naïve or prior null	Fixed-dose combination ledipasvir/sofosbuvir ± RBV responders, with or without cirrhosis	98.4 (1,872/1,902)	98.0 (1,864/1,902)	97.3 (1,850/1,902)
Lawitz, et al.[18]	n = 590 adults, HCV GT1-6	Sofosbuvir + RBV ± peg-IFN*	NR	NR	NR
Lawitz, et al.[19]	n = 42 adults, HCV GT1b Treatment-naïve, no evidence of cirrhosis Excluded HIV or HBV co-infection	Paritaprevir/ritonavir + dasabuvir x 12 weeks	97.6 (41/42)	95.2 (40/42)	92.9 (39/42)
Zeuzem, et al.[21]	n = 362 adults, HCV GT1 Treatment-naïve, with or without	Faldaprevir + deleobuvir ± RBV x 16, 28, or 40 weeks cirrhosis	NR	69	NR

** n = 33 received sofosbuvir + ledipasvir + RBV. GT: genotype. HBV: hepatitis B virus. HIV: human immunodeficiency virus. NR: not reported. PEG-IFN: peg-interferon. RBV: ribavirin. SVR: sustained virologic response.*

Table 2. Concordance of SVR4, SVR12 and SVR24.

Study	Antiviral regimen		PPV (%)		NPV (%)	
			SVR12	SVR24	SVR12	SVR24
Poordad, *et al.*[14]	GT1: paritaprevir/ritonavir, ombitasavir, dasabuvir +RBV for 12 or 24 weeks	SVR4 SVR12	99.2 -	97.5 98.3	100.0 -	100.0 100.0
Yoshida, *et al.*[16]	GT1, 4-6: sofosbuvir + PEG-IFN/RBV for 12 weeks GT2: sofosbuvir + RBV for 12 weeks	SVR4	GT1,4-6: 98.0 GT2: 97.8 GT3: 97.7	GT1,4-6:98.0	GT1-6: 100.0	GT1,4-6:100.0
	GT3: sofosbuvir + RBV for 24 weeks	SVR12 -		GT1, 2, 4-6: 100.0 GT3: 99.1	-	GT 1-6: 100.0
Bernstein, *et al.*[17]	GT1: ledipasvir/sofosbuvir ± RBV	SVR4 SVR12	99.6 -	98.8 100.0	100.0 -	100.0 100.0
Lawitz, *et al.*[18]	GT1-6: sofosbuvir+ RBV ± PEG-IFN	SVR4 SVR12	98.5 -	99.0 99.8	96.2 -	94.6 97.5
Lawitz, *et al.*[19]	GT1b: paritaprevir/ritonavir + dasabuvir	SVR4 SVR12	100.0 -	95.1 97.5	100.0 -	100.0 100.0
Zeuzem, *et al.*[21]	GT1: faldaprevir + deleobuvir ± RBV	SVR4 SVR12	95.0 -	NR 100.0	NR -	NR NR

GT: genotype. NPV: negative predictive value. NR: not reported. PEG-IFN: peg-interferon. PPV: positive predictive value. RBV: ribavirin. SVR: sustained virologic response.

subjects treated with sofosbuvir and RBV for 24 weeks, the negative predictive value of SVR12 was 100% whereas the positive predictive value dropped slightly to 99.1%. This was attributed to relapse in 2 treatment-experienced subjects without cirrhosis between post-treatment weeks 12 and 24. Based on the concordance analysis, the authors conclude that SVR12 is an appropriate efficacy endpoint for evaluation of sofosbuvir-containing regimens across all HCV genotypes and that SVR4 would not be suitable given the risk of relapse between weeks 4 and 12.[16] They also highlighted that the high concordance between SVR12 and SVR24 in their analysis was demonstrated with sofosbuvir-containing regimens with or without peg-IFN and may not be extrapolated to other new DAA regimens, especially those with shorter treatment duration and/or lower barriers to resistance.[16]

Bernstein, *et al.* performed a post-hoc concordance analysis of the SVR rates in phase III clinical trials (ION-1, ION-2, ION-3) for the all oral fixed-dose combination of sofosbuvir and ledipasvir with or without ribavirin.[17] In total, 1902 and 1853 subjects had SVR assessments available at post-treatment weeks 4 and 12 and weeks 12 and 24, respectively. Overall, the relapse rate was 2% (36 patients) with 78% of relapses occurring at or before post-treatment week 4. Eight subjects relapsed between weeks 4 and 12 whereas no relapses occurred after post-treatment week 12. Data for SVR rates and concordance analysis are summarized in tables 1 and 2.

Lawitz, *et al.* have published in abstract form the results of two SVR concordance analyses.[18,19] Similar to the analysis by Yoshida, *et al*.[16] Lawitz, *et al.* evaluated the concordance of SVR4 with SVR12 and SVR24 in studies of sofosbuvir-containing regimens as part of the phase II development program (PROTON, ELECTRON, ATOMIC, QUANTUM studies). Eight patients who had achieved SVR4 subsequently relapsed by 12 weeks post-treatment. One patient who had achieved SVR12 relapsed at week 24 post-treatment. Predictive values are tabulated in table 2.

A second abstract by Lawitz, *et al.*[19] outlines an exploratory concordance analysis of SVR rates for the 42 treatment-naïve subjects infected with HCV genotype Ib in the phase IIb trial PEARL-1 that evaluated the safety and efficacy of paritaprevir/ritonavir plus dasabuvir.[20] SVR4, SVR12 and SVR24 rates for the treatment-naïve subgroup are listed in table 1. Results of the concordance analysis are listed in table 2. There were no relapses through post-treatment week 24 and the observed discordance between SVR12 and SVR24 rates is a result of lack of data due to early discontinuation of 1 patient from the trial.

Zeuzem, *et al*.[21] analyzed data from the SOUND-C2 trial, which investigated the IFN-free combination of faldaprevir and deleobuvir in treatment-naïve patients with HCV genotype 1. HCV RNA was measured at weeks 4, 12, 24, and 48 weeks post-treatment. SVR12 rates were up to 69% in the overall population and 85% in those with genotype 1b. No relapses occurred between SVR12 and SVR24 and SVR12 had a positive predictive value of 100% for SVR24. One patient relapsed between SVR12 and SVR48 time points resulting in a positive predictive value of 98-100%.

DISCUSSION

Although several trials have demonstrated similar rates of SVR at post-treatment weeks 12 and 24, the purpose of the summarized articles above was to specifically evaluated concordance between the various post-treatment time-points. The available data suggests that SVR12 is a reliable assessment of HCV eradication and could be used instead of SVR24 for drug development clinical trials assessing efficacy of new DAAs and as reliable interim end-point in clinical practice although a 24 week post-treatment HCV determination would still be recommended. Overall, the studies summarized showed similarly high positive (> 97%) and negative (> 94%) predictive values. The data also demonstrates that the reliability of SVR12 to predict SVR24 has been validated in several populations infected with HCV (treatment-naïve, prior null responders, various genotypes) using various new oral DAA regimens. Currently, SVR4 would not an appropriate efficacy endpoint due to the higher risk of HCV relapse occurring after post-treatment week 4. These findings are similar to those in the retrospective analysis by Chen, *et al.* which found that the assessment between SVR4 and SVR24 demonstrated lower concordance with a positive predictive value of 91-93%.[10] The high concordance between SVR12 and SVR24 is consistent with viral kinetic and simulation studies that show that the majority of virologic relapses occur within 12 weeks after the end of treatment.[11]

There are some limitations of the available data that should be noted. One limitation is the generalizability of the SVR data to populations that were not studied. Most of the articles presented summarized clinical trial data that had excluded more difficult-to-treat populations including those co-infected with the human immunodeficiency virus or hepatitis B virus, post-transplant and those with evidence of cirrhosis. Two of the articles[16,17] mention that subjects that were lost to follow-up or did not have an SVR24 assessment available were not included in the concordance analyses therefore it is possible that the concordance between SVR12 and SVR24 may have been slightly overestimated. It is important to note that most the data is from clinical trials examining sofosbuvir-based regimens or the combination regimen of paritaprevir/ritonavir with dasabuvir ± ombitasavir and it will be essential to

confirm concordance of SVR12 with SVR 24 with new DAA regimens. Finally, given the relatively short duration of clinical trials, longer follow-up studies are required to determine the durability of the SVR response with newer DAA regimens, especially those that involve shorter treatment durations. For example, an interim analysis of long-term follow-up of patients who were treated with sofosbuvir-based regimens in phase III studies have shown maintenance of SVR through a median follow-up of 24 weeks[22] but data on the durability over several years is needed.

CONCLUSION

Sustained virologic response defined as HCV RNA ≤ 25 IU/mL by a sensitive assay determined at post-treatment week 12 shows high concordance to SVR rates at post-treatment week 24 with new DAAs regimens. SVR12 is therefore an appropriate primary efficacy endpoint for regulatory approval trials to deem HCV eradication. Currently, SVR4 is not suitable due to the risk of relapse post-treatment week 4. SVR registry studies in progress will provide important information about the durability of SVR12 following treatment with oral DAAs and the incidence of relapse.

ABBREVIATIONS

- **DAA:** direct-acting antivirals.
- **HCV:** hepatitis C virus.
- **peg-IFN:** pegylated interferon.
- **RBV:** ribavirin.
- **RNA:** ribonucleic acid.
- **SVR:** sustained virologic response.

FINANCIAL SUPPORT

This review was completed without the help of grants or financial support.

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