Sustained virological response 12 versus sustained virological response 24 as evaluation endpoints in chronic hepatitis C virus Egyptian patients treated with sofosbuvir-based regimens

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Background
The recommended reliance on 12 weeks posttreatment sustained virological response (SVR12) instead of SVR24 was validated for treatment evaluation.
Aim
Judging claimed concordance between SVR12 and SVR24.
Patients and methods
In a prospective study, 91 patients received sofosbuvir (SOF)+interferon+ribavirin (RV) for 12 weeks; 52 patients received SOF+RV for 24 weeks; and 56 patients received SOF+simeprevir for 12 weeks. Demographic and laboratory data, transient elastography, treatment regimens, hepatitis C virus RNA at week 4, week 12, and SVR12 and were reported. Patients who failed to achieve undetectable hepatitis C virus RNA at the end of therapy were excluded.
Results
Concordance between SVR12 and SVR24 was 96.5%, with a positive predictive value of 96.4%. Regarding treatment groups it was found to be 95.6% for SVR24 in SOF+interferon+RV-treated patients, 94.2% in SOF+RV-treated patients, and 100% concordance in SOF+simeprevir-treated patients with insignificant values (P=0.2). In spite of nonsignificance, the reported seven (3.5%) relapsers were mainly male gender (five cases, P=0.9), naïvely treated (five cases, P=0.6), achieved rapid virological response (five cases, $P>0.005$), with advanced fibrosis (F4) by fibroscan (five cases, P=0.7). Regression analysis failed to detect any predictors of relapse.
Conclusion
In spite of the high grade of concordance between SVR12 and SVR24, the reported rate of relapsers necessitates the backward commitment to SVR24 as a reliable primary endpoint of treatment response evaluation.

Keywords:
SVR12, SVR24, HCV, DAAs

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Introduction

Hepatitis C virus (HCV) is represents a global public health problem, with an estimated worldwide burden exceeding 160 million (2.3% of the world population) [1]. Egypt had been notified as the highest country burdened with HCV all over the world (14.7%) [2].

For more than two decades, interferon (IFN) had been the basis for chronic HCV treatment. Responses to treatment were improved in 1998 by the addition of ribavirin (RV) and then in 2001–2002 by linking the IFN molecule to polyethylene glycol [3].

The advent of direct-acting antiviral (DAAs) agents had led to the replacement of IFN with well-tolerated oral therapies and higher cure rates of more than 90% in most studied populations [4].

During the IFN era, the standard endpoint of outcome was to achieve undetectable HCV RNA at 24 weeks after the end of treatment [sustained virological response (SVR24)]. This was based on both the continued durability of viral suppression beyond 24 weeks and the rare occurrence of relapse [5].

A lot of durability studies had been accomplished, checking SVR24 for at least 4 years, with convenient grantee of its ability to be the follow-up end point of HCV treatment, crowning it as a gold standard [6–8].

However, the craving for shorter follow-up periods and early detection of relapsers along with better economics had justified the search of earlier SVR relevant.

Zeuzem *et al.* [9], in the era of non-pegylated IFN and Martinot-Peignoux *et al.* [10], in the era of pegylated IFN were the uprising premieres, suggesting the possibility of utilizing SVR at 12 weeks posttreatment (SVR12) for substituting SVR24 as an early hallmark of viral elimination. Despite the clinical invalidity at these times, their results were an early notion of a new definition of SVR.

In the era of DAAs, an urge for more creational evolutions in treatment strategies modulating management policies and optimizing their therapeutic benefits was mandated. Consequently, the revolution to SVR12 was reinvestigated, comparing its accuracy of being the hallmark of viral clearance to SVR24 post-DAA therapy.

In 2013, the regulatory authorities (the American Association for the Study of Liver Diseases and Infectious Diseases Society of America) had approved SVR12 to be the follow-up endpoint following a large study based on data assessment of 15 phase II and III trials, three pediatric studies, and five drug-development programs to determine the concordance between SVR24 and SVR12 or SVR4. However, the resultant concordance was mostly restricted to genotypes 1, 2, and 3 [11].

So, this study was designed to evaluate the concordance between SVR12 and SVR24 posttreatment with three sofosbuvir (SOF)-based regimens in a cohort of Egyptian patients who are predominantly genotyped 4a.

Patients and methods

This prospective study was conducted on 199 genotype 4 chronic HCV patients, eligible for DAAs therapy. They were randomly collected from the Virology Clinic of the National Liver Institute, Menoufia University as an Egyptian Governmental Accredited Center for HCV DAAs therapy from August 2015 to June 2016.

All patients were recruited according to the enlisted criteria of the international guidelines for HCV treatment regarding different treatment regimens. Approval from the ethics committee of the National Liver Institute, Menoufia University, along with patients' written consent were prerequisites for recruitment in this study. All demographic, pretreatment and posttreatment laboratory, and imaging data were collected from patients' records including; age, sex, liver function tests, complete blood picture, prothrombin time, international normalized ratio, abdominal ultrasonography, and transient elastography.

Exclusion criteria

(1) Age less than 18 years or more than 70 years.
(2) Hepatitis B virus or HIV coinfection.
(3) Failure to complete a full course of therapy due to any cause; patient incompliance, intractable drug-induced complications necessitating drug stoppage like severe drug reaction/allergy, incompatible fatigue, clinical, or laboratory hepatic decompensation.
(4) Patients who missed follow-up were excluded.
(5) Failure to achieve an end of treatment virological response (defined as undetectable HCV RNA at the end of therapy). Accordingly, the initial number of enlisted and followed-up cases was 250. Cases with incomplete data, failure to complete treatment, or unachieved SVR12 were eliminated. The actual contributors in this study were 199 cases. They were followed up to 24 weeks postend of treatment. The patients were categorized into three groups according to their treatment regimens:
   (a) Group I: 91 cases were given SOF in combination with peg-IFN and RV for 12 weeks. SOF was administered 400 mg once daily, peg-IFN-2a 180 subcutaneously once weekly, and weight-based RBV (1000 mg/day for $<$75 kg and 1200 mg/day for $\geq$75 kg in two divided doses).
   (b) Group II: 56 cases received SOF in combination with RV for 24 weeks. SOF was administered at 400 mg once daily, and weight-based RBV dose at 1000 mg/day for $<$75 kg and 1200 mg/day for $\geq$75 kg in two divided doses.
   (c) Group III: 52 cases received daily 400 mg SOF and 150 mg simeprevir (SIM) for 12 weeks.

Statistical analysis

Data were collected and entered into the computer using the Statistical Package for the Social Sciences program for statistical analysis (version 13; SPSS Inc., Chicago, Illinois, USA). Data were entered as numerical or categorical, as appropriate. Two types of statistics were done: descriptive and analytical. χ^2 test was used to measure the association between qualitative variables. Fisher's exact test was used for

2×2 qualitative variables when more than 25% of the cells have an expected count of less than 5. Student's *t* test was used to compare mean and SD of two sets of quantitative normally distributed data, while Mann–Whitney test was used when this data is not normally distributed. Paired *t* test was used to compare mean and SD of paired quantitative normally distributed data, while Wilcoxon's test was used when this data is not normally distributed. McNemar's test was used to compare two proportions that were related to each other. *P* value was considered statistically significant when it was less than 0.05. Positive predictive value (PPV) and negative predictive value (NPV) of SVR12 for SVR24 were performed using these equations: PPV=the proportion of a test's positive results that are truly positive (TP)=TP/(TP+FP), while NPV=the proportion of negative test results that are truly negative (TN)=TN/(TN+FN).

Results

Regarding SVR24 achievement, 192 (96.5%) patients had SVR24, while the remaining seven (3.5%) patients did not achieve it, labeled as late relapsers with a PPV of 96.4% (Table 1). Patients who achieved SVR24 were 87 (95.6%), 49 (94.2%), 56 (100%) in groups I, II, III, respectively, while relapsers were four (4.4%), three (5.8%), 0 (0%) in groups I, II, III, respectively. In spite of the absence of significant statistical difference between the studied groups ($P>0.05$), the numerical difference cannot be ignored (Fig. 1).

Regarding pretreatment characters of the studied cases

Aspartate transaminase was 61.01±43.9 in SVR24 positive patients, 85±51.42 in SVR24 negative patients, with no statistically significant difference ($P>0.05$). With regard to pretreatment alanine transaminase (ALT), its average value was 66.76 ±62.71 in SVR24 positive patients, 63.71±23.56 in SVR24 negative patients, with no statistically significant difference ($P>0.05$). Concerning pretreatment bilirubin, it was 0.844±0.45 in SVR24 positive patients, 0.925±0.473 in SVR24 negative patients, with no statistically significant difference ($P>0.05$). Regarding alpha fetoprotein, its mean value was 13.53±25.94 in SVR24 positive patients, 21.75±12.68 in SVR24 negative patients, with no statistically significant difference ($P>0.05$). The hemoglobin in patients who achieved SVR24 was 13.52±1.96 g/dl, and 12.08±1.88 g/dl in patients who did not achieve it. Regarding platelet counts, it was 167.74±68.3 in patients who achieved SVR24 and 154.29±66.288 in patients who did not achieve it. There is no statistically significant difference between the two groups regarding all elements of complete blood picture ($P>0.05$). Concerning pretreatment stiffness measurements, it was 17.45 ±13.52 kDa in patients who achieved SVR24 and 19.614±11.88 kDa in patients who did not achieve it but with no significant difference between the two groups. A notion to be mentioned: they were higher in relapse patients ($P>0.05$). With regard to pretreatment fibrosis 4, it was 3.127±2.29, 4.87 ±4.002 in groups I and II, respectively, with an insignificant difference ($P>0.05$) (Table 2).

Regarding rapid virological response (RVR), IFN–SOF–RV group who achieved RVR had a PPV of 97.3% to achieve SVR24 and patients who did not achieve it have an NPV of 13.3%.in the SOF–RV group. Patients who achieved RVR have a PPV of 93.8% to achieve SVR24. Concerning the SOF–SIM group, patients who achieved RVR have a PPV of 100% to achieve SVR24 (Fig. 2).

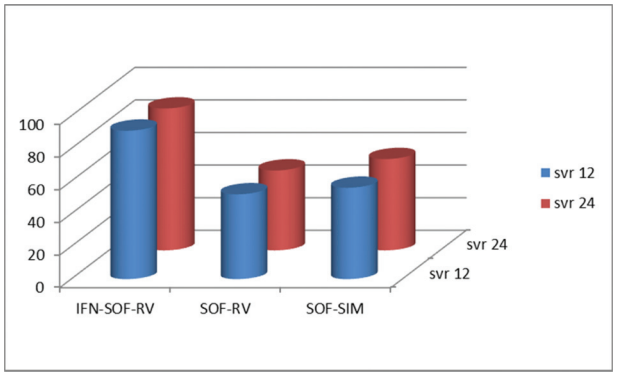
Regarding the seven relapse characteristics: their mean age was 54.86±3.7 years, consisting of five (71.4%) males and two (28.6%) female patients with no statistical significance ($P>0.05$). Regarding treatment experience, five (71.4%) of the relapse patients were treatment naïve, while the remaining

Table 1 Concordance of sustained virological response 12 and sustained virological response 24

SVR	SVR at 24 weeks		PPV (%)	NPV (%)
	Yes (*n*)	No (*n*)		
SVR at 12 weeks (*N*=199)				
Yes	192	7	96.4	0
No	0	0		

PPV, positive predictive value; SVR, sustained virological response.

Figure 1



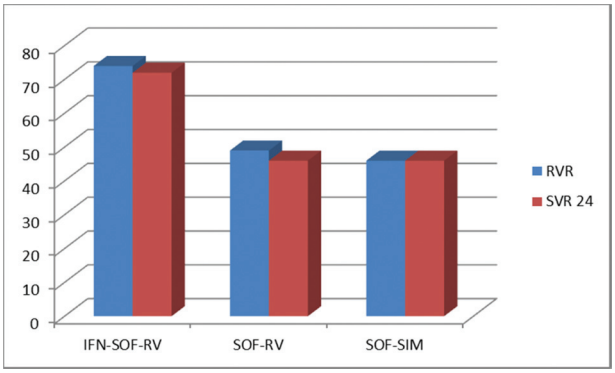
Concordance of SVR12, SVR24 in the three treatment groups: SVR, sustained virological response.

Table 2 Pretreatment characteristics and sustained virological response 24

	SVR24		Test	*P* value
	Yes (*N*=192)	No (*N*=7)		
	Mean±SD			
AST (IU/l)	61.01±43.9	85±51.42	0.478	> 0.05
ALT (IU/l)	66.76±62.71	63.71±23.56	0.302	>0.05
Bil (mg/dl)	0.844±0.45	0.925±0.473	0.745	>0.05
AFP (IU/l)	13.53±25.94	21.75±12.68	0.856	>0.05
Hb (g/dl)	13.52±1.96	12.08±1.88	0.580	>0.05
ANC ($\times 10^3/mm^3$)	2.93±1.03	2.9±0.86	0.437	>0.05
Platelets ($\times 10^3/mm^3$)	167.74±68.3	154.29±66.2	0.760	>0.05
HCV PCR (IU)	514 693.89±280 233.3	480 163.57±631 690.8	0.813	>0.05
Stiffness (kPa)	17.45±13.52	19.614±11.88	0.142	>0.05
Fibrosis 4 score	3.127±2.29	4.87±4.002	4.44	>0.05

AFP, alpha fetoprotein; ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; Bil, bilirubin; Hb, hemoglobin; HCV, hepatitis C virus; SVR, sustained virological response.

Figure 2



The relationship between RVR, SVR24 among treatment groups: RVR, rapid virological response; SVR, sustained virological response.

two (28.6%) patients were treatment experienced, four (57.1%) of them belong to group I, three (42.9%) belong to group II while no one belongs to group III with no statistical significance (*P*>0.05). Regarding laboratory finding in relapse patients, the mean of PCR count in relapse patients was 480 163.57±631 690.8, their mean ALT was 63.7±23.5, aspartate transaminase 85.0±51.4, bilirubin 0.92±0.47, alpha fetoprotein 21.7 ±12.6, hemoglobin 12.08±1.8, white blood cells 5.7 ±1.8, and platelet was 154.2±66.2 with no significant factor being able to predict relapse (*P*=0.05) (Table 3). Regarding achievement of RVR, two (28.5%) patients and three (42.8%) patients in groups I and II, respectively, who achieved RVR were relapsers while two (28.5%) patients of group I did not achieve RVR and were relapsers (*P*>0.05) (Table 3). Concerning the stiffness scores of relapse patients, no one belonged to F0 or F1, one (14.3%) patient was F2, one (14.3%) patient F3, five (71.4%) patients were F4 with no significant difference. Most relapsers were cirrhotic (*P*>0.05) with a mean stiffness score of 19.6±11.8 KPa (Table 3).

Regarding predictors of relapse, naïve patients are more protected from relapse than experienced patients, while patients with an ALT level of more than 80 are at two and half time more at risk to develop relapse. F4 patients are three and half times more at risk to develop relapse but not significant (*P*>0.05) (Table 4).

Discussion

Analyzing the patients' data showed a relatively clear high grade of concordance between SVR12 and SVR24. All patients were SVR12 according to the inclusion criteria, 192 (96.5%) of them had achieved SVR24 with a PPV of 96.4%. In spite of being insignificant, the 3.5% discordance (seven relapsers) is representing overlooked late relapsers. They exemplify a hidden infectious focus, hindering all epidemiological efforts of disease control added to the predestined occurrence of cirrhosis with its comorbid complications.

This was relatively close to the results of the Japanese study which was conducted on 46 patients on telaprevir and SIM with or without peg-IFN plus RV. They reported four relapsers in the SIM group, recommending the reuse of SVR24 for predicting treatment outcome on using protease inhibitors with peg-IFN plus RV [12]. Also, a big meta-analytic study was conducted on MEDLINE, Embase, and Cochrane CENTRAL for 35 randomized clinical trials with a peg-IFN-RV arm that used SVR24 and/or SVR12. Using meta-regression, the pooled SVR12 was 6% higher than SVR24 with peg-IFN alpha-2a (53 vs. 47%) and 5% higher with peg-IFN alpha-2b (45 vs. 40%). They recommended back to SVR24, for a safer interpretation [13].

SVR24 achievement was accomplished in 87 (95.6%) patients of the IFN–SOF–RV-treated group with a

Table 3 Characteristics of relapsers

Demographic data	Relapsed patients	Fischer exact test	*P* value
Age (years)			
Mean±SD	54.86±3.7	0.495*	0.621
Sex [*n* (%)]			
Male	5 (71.4)	0.003	0.995
Female	2 (28.6)		
Treatment status [*n* (%)]			
Naïve	5 (71.4)	0.477	0.616
Experienced	2 (28.6)		
RVR achievement [*n* (%)]			
Yes	5 (71.4)	0.27	>0.005
No	2 (28.6)		
Treatment regimen [*n* (%)]			
IFN–SOF–RV (I)	4 (57.1)	3.02	0.220
SOF–RV (II)	3 (42.9)		
SOF–SIM (III)	0 (0.0)		
PCR (IU/l)	480 163.57±631 690.8	1.46	0.142
ALT (IU/l)	63.7±23.5	0.835	0.404
AST (IU/l)	85.0±51.4	1.41	0.157
Bilirubin (mg/dl)	0.92±0.47	0.687	0.492
AFP (IU/l)	21.7±12.6	2.439	0.015
Hb (g/dl)	12.08±1.8	1.84	0.065
WBCs ($\times 10^3/mm^3$)	5.7±1.8	0.652	0.515
Platelet ($\times 10^3/mm^3$)	154.2±66.2	0.337	0.736
Fibroscan stiffness (kPa)	19.6±11.8	0.902	0.367
Fibrosis 4 score	4.8±4.0	1.112	0.266

AFP, alpha fetoprotein; ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; Bil, bilirubin; Hb, hemoglobin; IFN, interferon; RV, ribavirin; RVR, rapid virological response; SIM, simeprevir; SOF, sofosbuvir; WBC, white blood cell.

PPV of 95.6%, 49 (94.2%) patients of the SOF–RV-treated patients with a PPV of 94.2%, while all patients (100%) treated with SOF/SIM had achieved an SVR24 with 100% PPV.

Kowdley *et al.* [14] had supported these results with the high grade of concordance reported in IFN or RV-free regimens, with little discordance in IFN or RV containing regimens. All patients were able to achieve SVR12 with a PPV of 97.3% to achieve SVR24 in the IFN–SOF–RV group, 93.8% in the SOF–RV group, and 100% in the SOF–SIM group, a notion supported by the accelerated advent of IFN-free regimens all over the world. The next step to be anticipated and mandated is the prospect of RV-free regimens. A move which had been evaluated by two eminent studies assessed the efficacy of a SOF/SIM or SOF/daclatasvir combination with or without RV in genotype 1 patients with or without cirrhosis. They negated any role of the addition of RV in improving SVR, added to the manifest side effects [15,16]. However, a more apprehensive research in large-sized clinical trials is still needed to elucidate this debatable issue.

Table 4 Binary logistic regression for factors affecting sustained virological response 24

	Odd's ratio	*P* value
Treatment status (naïve)	0.45	0.35
ALT>80	2.47	0.37
Fibrosis scan (F4)	3.34	0.17

Factors entered the equation are: age, sex, treatment status, treatment regimen, rapid virological response, and fibrosis stage, Alb, alanine transaminase, aspartate transaminase, bilirubin, Pc, platelets, white blood cell, and absolute neutrophil count.

On the other hand, a lot of durability studies had opposed our results. For instance, the SPARE trial, which had reported an identical (100%) concordance between SVR12 and SVR24 in GT1 patients who received SOF and RBV for 24 weeks [17]. Also Yoshida *et al.* [18] who performed a retrospective concordance analysis of SVR rates in five phase III clinical trials (NEUTRINO, FISSION, POSITRON, FUSION, and VALENCE) that assessed the efficacy of SOF-containing regimens in patients with known virological outcomes; 99.7% of patients that achieved SVR12 had achieved SVR24.

Bernstein *et al.* [19] mentioned a 100% PPV in concordance analysis of SVR rates: 4-12-24 in phase III clinical trials for the oral fixed-dose combination of SOF and ledipasvir with or without RV. Lawitz *et al.* [15] evaluated the concordance of SVR12 and SVR24 in SOF-containing regimens as part of phase II development program with proved 99.8% PPV. Also, Zeuzem *et al.* [20], had analyzed data from the SOUND-C2 trial. They investigated the IFN-free combination of faldaprevir and delcobuvir in treatment-naïve genotype I HCV patients, without any relapse between SVR12 and SVR24.

In this study, RVR (absence of viremia after 4 weeks of treatment) was reached in 85% of patients which had abrogated the importance of RVR in the prediction of SVR12 or SVR24.

These results were dissimilar to what was mentioned in Marcellin *et al.* [21], who considered a virological response by week 4 had the highest PPV for SVR24 among patients infected with HCV genotypes 1 or 4. Manns *et al.* [22], also stated that in IFN-based therapies including a protease inhibitor like SIM, RVR is highly predictive of SVR12.

However, our results were supported by Poordad *et al.* [23], who proved that RVR did not predict outcome as all patients had achieved this benchmark in their study. Consequently, the clinical relevance of this point is minimized for just prediction of a small number of nonresponders with no treatment stoppage decisions relied upon.

Nevertheless, the advent of shorter duration DAAs regimens necessitates the evaluation of earlier time points (e.g. week 1 or week 2) not only for predicting treatment outcomes but also for narrowing treatment durations.

It is also noteworthy to mention that all patients who belonged to the SOF–SIM group had achieved RVR. A note which might shed more lights on the enhanced efficacy of using new DAAs therapies without peg-IFN and/or RBV [24].

Talking about relapsers in our study, the seven (3.5%) relapsing patients were four cases in IFN–SOF–RV and three cases in the SOF–RV groups with none in the SOF–SIM group as mentioned before.

In this study, we had 162 (81.4%) naively treated patients and 37 (18.6%) had experienced INF/RBV treatment before with nonresponse. Unsurprisingly, 96.9% of the naive patients had reached SVR24, while five (3%) patients could not. In the experienced group, 94.5% of them had reached SVR24 with only two relapsers. The SVR24 of the treatment-experienced patients in the SOF–SIM group was 100%. Adding a robust proof of the more efficacy of the INF/RBV-free regimens especially in this difficult to treat population [24].

Again, the occurrence of seven relapsers in our cohort questioned the efficacy of SVR12 in a mostly genotype 4 Egyptian cohort, treated with SOF-based regimens along with INF and/or RBV. Commitment to SVR12 means those relapsers will be missed, veiled in the community, with inevitable progression of liver disease to cirrhosis with its morbid complications. They will also represent a hidden source of continuous infection spread.

Although it would be of interest to determine factors predicting late relapse between weeks 12 and 24, the limited number of cases (only seven) hindered any meaningful analysis. However, it was noticed that cirrhotic patients and those with an ALT level of more than 80 IU/l were more liable to relapse, while naïve patients were protected from relapse than experienced cases.

Dissimilarly, Osinusi *et al.* [17], had reported male sex, advanced liver disease, and high baseline HCV RNA as predictors of relapse occurrence.

Conclusion

In conclusion, this analysis negated the validity of SVR12 as an appropriate efficacy endpoint for the evaluation of regimens containing SOF plus peg-IFN/RBV and SOF plus RBV. On the other hand, its validity is mounted in DAAs regimens free of IFN and RBV.

It is unknown whether new DAAs regimens, particularly those with shorter durations and/or with drugs with lower barriers to resistance, will demonstrate similar concordance or not.

The near future research must emphasize much more on long-term virological outcome follow-up studies in regimens of shorter durations along with IFN-RV-free protocols. Further studies have to be replicated to determine the long-term durability of SVRs.

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Conflicts of interest

There are no conflicts of interest.

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