Sustained Virologic Response to Antiviral Therapy for Chronic Hepatitis C Virus Infection: A Cure and So Much More

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Sustained virologic response (SVR) is defined as aviremia 24 weeks after completion of antiviral therapy for chronic hepatitis C virus (HCV) infection. In analyses of SVR durability, the incidence of late relapse is extremely low (<1%). Histologic regression of both necroinflammation and fibrosis has been demonstrated in paired liver biopsy samples in SVR-achieving patients. More noteworthy is the sustained responder's favorable prognosis even with baseline cirrhosis; despite mostly retrospective analyses, relative to nonresponders or to those untreated, patients with SVR have significantly fewer liver-related complications, less hepatocellular carcinoma, and fewer liver-related deaths. Although HCV is associated with insulin resistance, successful eradication of HCV appears to reduce the risk of impaired fasting glucose and diabetes development. In summary, chronic HCV infection is curable with SVR attainment, and with cure comes improved liver histology and more favorable clinical outcomes, in comparison with patients who do not achieve the same therapeutic milestone.

More than 170 million persons worldwide are infected with hepatitis C virus (HCV) [1], and it has become the leading cause of death associated with liver disease in the United States [2]. Moreover, the incidence of HCV-related hepatocellular carcinoma (HCC) and hepatic decompensation is expected to increase for at least another 2 decades; liver-related deaths are expected to increase to 283,378 during 2020–2029 from 56,377 deaths during 1990–1999 [3].

The sustained virologic response (SVR) has become the best indication of successful therapy for HCV infection; SVR is defined as an absence of detectable HCV RNA in the serum with use of an assay with a sensitivity of at least 50 IU/mL 6 months after therapy is complete [4, 5]. Although there is some support for the identification of SVR as early as 12 weeks after treatment [6, 7], the 24-week posttherapy determination of SVR remains the gold standard for treatment success [5]. With the current standard of care, pegylated interferon and ribavirin, patients with chronic HCV infection can achieve SVR 54%–56% of the time [8, 9].

SVR has been labeled a surrogate therapeutic end point, because until recently, accompanying clinical outcome data were scant. The purpose of this review is to summarize evidence supporting SVR as a durable and clinically meaningful end point of successful antiviral therapy.

METHODS

Data were identified by searching MEDLINE from inception to December 2010 and from recent major clinical meetings in English. Search terms included "HCV," "SVR," "long-term outcome," "histology," "advanced fibrosis," "cirrhosis," "HCC," "complications," "mortality," "diabetes," and "impaired fasting glucose."

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SVR and Cure

Several studies have addressed HCV infection recurrence after antiviral therapy–induced SVR. The data are difficult to compare, because the patient' age, sex, ethnicity, viral genotype, and baseline histology differ among publications. Moreover, the dose, duration, and interferon formulation and the inclusion of ribavirin also differ among studies of recurrence. Lastly, the duration of follow-up and the assays used to study recurrence are likewise dissimilar.

Despite the study disparities, the rate of late relapse, defined as reappearance of serum HCV RNA, is extremely low, with the majority of studies showing 0%–1% (Table 1). Two preliminary studies, from Egypt [26] and Italy [20], showed late relapse rates of 9% and 10%, respectively. It is unclear why these studies demonstrated higher late relapse rates relative to multiple other reports with even longer duration of follow-up; however, 90% of patients in the Egyptian study were genotype-4 infected, a group for which long-term follow-up data are scarce. Nonetheless, it is reassuring that the largest prospective cohort of patients followed up for SVR durability ($n = 1343$) from 9 randomized multicenter treatment trials using pegylated interferon showed a late relapse rate of .8% [19].

Because the aforementioned studies did not use detailed viral molecular analysis, it is unclear how many cases of late relapse were actually cases of reinfection. In some instances, such as in intravenous drug users (IVDU), re-exposure seems to be the basis for recurrence. In a study from Munich and New York, 18 IVDUs were successfully treated for HCV infection, but 2 patients (11%) became reinfected as a result of illicit drug use [30]. The authors estimated rate of reinfection in this cohort was 0%–4.1% cases per 100 person-years, which is consistent with a previously published Norwegian study of IVDUs (2.5 cases per 100 person-years) [31].

SVR longevity has also been confirmed in HCV-infected liver transplant recipients [32–34], hemophiliacs [35], cirrhotics [13], those coinfected with HIV [36], and children [37].

With the advent of sensitive assays capable of detecting HCV RNA at low quantities, clinically hidden but molecularly apparent HCV infection has been identified [38]. The description of occult HCV has challenged the notion that therapeutically induced resolution of HCV is permanent; however, this concept is controversial [39]. Except for rare cases of residual HCV RNA detected in peripheral blood monocytes and in liver tissue [40–43], the clinical significance of which is doubtful, SVR is associated with viral clearance [11, 44–47]. To date, there has been no published report of a patient with occult HCV infecting a previously uninfected individual.

In summary, data support SVR durability with minimal rates of late relapse. Available evidence suggests that a SVR is tantamount to HCV infection cure.

Benefits of SVR

Histologic Benefits. The vast majority of SVR-achieving patients demonstrate histologic improvements on posttreatment biopsies relative to pretherapy (Table 2). Both fibrosis (stage) and inflammatory activity (grade) usually regress. In fact, some authors have reported complete resolution of fibrosis or of portal inflammation after SVR [10, 11, 46, 48, 53, 55].

Histologic improvement is not limited to immunocompetent patients; it has been demonstrated in HIV-HCV–coinfected patients [56, 57] and in orthotopic liver transplant recipients [33, 34].

Seven studies have shown that regression of HCV-related cirrhosis is possible with achievement of SVR (range, 8%–75%) [10, 12, 46, 48, 49, 51, 58]. In one of them, virologic response was the only predictor of improvement in grade (odds ratio [OR], 23.7; 95% confidence interval [CI], 6.7–80.9) and in stage (OR, 2.16; 95% CI, 1.04–4.47) [49].

The scientific basis for fibrosis or cirrhosis reversal may lie in the biology of the liver's wound-healing response. Fibrosis represents a balance between hepatic extracellular matrix or scar formation and pathological matrix degradation in which the hepatic stellate cell (quiescent myofibroblasts) and inhibitors of matrix metalloproteinases play critical roles; the stellate cell increases scar formation and matrix production, and tissue inhibitors of matrix metalloproteinases (TIMPs) coordinate matrix degradation and impact stellate cell activation. With fibrosis regression, TIMP levels are decreased along with apoptosis-mediated clearance of activated stellate cells. In periods without liver injury, at least in animal studies, some fibrosis deposition will not regress, especially if the collagen matrix is significantly cross-linked or if the tissue contains thick collagen bands. This might explain why some of the HCV-related fibrosis cannot be reversed [59, 60].

Despite the encouraging aforementioned results, of note, histologic analysis is fraught with bias, including sampling error and interobserver variability. Some of the authors listed in Table 2 tried to mitigate these factors by defining improvement in fibrosis as at least a 2-stage change, by using standard methods for fibrosis evaluation, by ensuring adequate specimen lengths (at least 1 cm, preferably 2.5 cm) [11, 46, 48, 49, 53, 54] and by using experienced hepatopathologists blinded to pretreatment biopsies [10, 12, 33, 49, 50, 52, 53, 55–57]. Although some of the aforementioned histologic studies can be criticized because of some of these factors, the overall uniformity of results suggest histologic amelioration with viral suppression, particularly with SVR.

Clinical Events and Survival. The effects of therapy on reducing liver disease complications and, therefore, mortality, have been difficult to prove. A multitude of studies have shown that liver-related complications, including decompensation, hepatocellular carcinoma, and liver-related death, are less

Table 1. Rates of Late Relapse among Patients Achieving Sustained Virologic Response (SVR) with Interferon-Based Therapy[a]

Therapy	No. of patients with SVR	Percentage with late relapse	Assay sensitivity	Duration of follow-up after therapy, months	Follow-up duration after therapy, range, months	Study, year (Reference)
IFN/RBV, PEG/RBV	150	0	5 IU/mL	61 (median)	12–93	George et al 2009 [10]
IFN, IFN-lymph	80	4	10 copies/mL	48 (mean)	12–90	Marcellin et al 1997 [11]
IFN, IFN-beta, IFN-lymph, IFN-hybrid, IFN/RBV, PEG/RBV	344	0	10 IU/mL	39 (median)	6–216	Maylin et al 2008 [12]
IFN	286	4.7	100 copies/mL	59 (mean)	12–120	Veldt et al 2004 [13]
IFN, IFN/RBV, PEG/RBV	87	8	100 copies/mL	NR	60–84	Pradat et al 2007 [14]
IFN	80	0	1,000–10,000 copies/mL	35 (mean)	18–48	Chemello et al 1996 [15]
IFN, PEG/RBV	278	0	10 IU/mL	56 (mean)	6–132	Martinot-Peignoux et al 2008[b][16]
PEG, PEG/RBV	366	1	100 copies/mL	57 (mean)	36–260	Manns et al 2008[b] [17]
IFN, IFN/RBV, PEG/RBV	75	0	NR	NR	36–108	Torres-Ibarra et al 2007[b] [18]
PEG, PEG/RBV	1343	0.9	50 IU/mL	47(mean)	10–85	Swain et al 2010[e] [19]
PEG/RBV	110	10	50 IU/mL	28 (median)	11–47	Basso et al 2007[b] [20]
IFN, IFN/RBV	492	1	100 copies/mL or 29 IU/mL[c]	65 (mean)	NR	McHutchison et al 2006[b] [21]
PEG/RBV	231	0.9	50 IU/mL	38 (median)	32–42	Giannini et al 2010 [22]
IFN, IFN/RBV, PEG/RBV	147	0.7	50 IU/mL	28 (mean)	4–124	Desmond et al 2006 [23]
IFN, IFN/RBV, PEG/RBV	187	0	50 IU/mL	29 (median)	12–172	Formann et al 2006 [24]
IFN, IFN-lymph, IFN-leuk	87	0	NR	NR	36–76	Toccaceli et al 2003 [25]
IFN/RBV, PEG/RBV	83	9	NR	37 (median)	26–44	El-Raziky et al 2006[b,d] [26]
IFN, PEG	171	0	100 copies/mL	35 (mean)	13–57	Chava-litdhamrong et al 2006 [27]
IFN, IFN/RBV, PEG, PEG/RBV	132	0	50 IU/mL	42 (mean)	12–156	Moreno et al 2006 [28]
IFN, IFN/RBV, PEG, PEG/RBV	103	2.9	NR	91 (median)	6–264	Koh et al 2010 [29]

Abbreviations. IFN, standard interferon alpha; IFN-leuk, leukocyte interferon-α; IFN-lymph, lymphoblastoid interferon; NR, not reported; PEG, pegylated interferon; RBV, ribavirin.

[a] Studies selected with a minimum of 75 previously treatment-naïve patients achieving sustained virologic response with a minimum mean or median follow-up of 24 months post-therapy.

[b] Preliminary data.

[c] After March 2001.

[d] Ninety percent had genotype 4 infections.

[e] One hundred patients were HCV-HIV coinfected.

Table 2. Histologic Benefits of Sustained Virologic Responders to Interferon-Based Therapy

Treatment	Patients studied*	Posttreatment time to biopsy, months	Staging system and minimum biopsy length	Improved inflammation (relative to pretherapy biopsy)	Improved fibrosis (relative to pretherapy biopsy)	Reference (number)
IFN, IFN-lymph	48	12–74	Knodell 1 cm	94%	0%	Marcellin et al 1997 [11]
IFN	110	19 (mean)†	Knodell NR	NR	28%	Veldt et al 2004 [13]
IFN, IFN/RBV, PEG, PEG/RBV	1094	20 (mean)†	Metavir 1.4 cm	86%	25%	Poynard et al 2002 [46]
IFN, IFN-beta	183	38 (median)†	Metavir 1.0 cm‡	89%	59%	Shiratori et al 2000 [48]
IFN, PEG	280	6 (mean)	Knodell 1.5 cm	81–82%	30–34%	Camma et al 2004 [49]
IFN, PEG	40§	20 (median)†	Metavir or Knodell NR	63%	50%	Everson et al 2008 [50]
IFN, IFN-beta, IFN-lymph, IFN-hybrid, IFN/RBV, PEG/RBV	126	6 (median)	Metavir 1.5 cm‖	57%	56%	Maylin et al 2008 [12]
IFN, IFN-lymph, IFN-leuk	87	30 (mean)	Knodell NR	87%	44%	Toccaceli et al 2003 [25]
IFN, IFN/RBV, PEG/RBV	39§	17 (median)	Metavir 1.5 cm‖	NR	49%	Mallet et al 2008 [51]
IFN/RBV, PEG/RBV	49	62 (mean)	Ishak NR	92%	82%	George et al 2009 [10]
IFN, IFN-lymph	47	48–72	Knodell NR	88%	38%	Bruno et al 2001 [52]
IFN	93	19 (mean)	Knodell 2 cm	98%	71%	Tsubota et al 1997 [53]
PEG/RBV	94	6	Ishak 1 cm	NR	26%	Balart et al 2010 [54]
IFN, IFN-leuk	21	60 (mean)	Scheur NR	100%	100%	Reichard et al 1999 [55]

ABBREVIATIONS. IFN, standard interferon alpha; IFN-leuk, leukocyte interferon-alpha; IFN-lymph, lymphoblastoid interferon; NR, not reported; PEG, pegylated interferon; RBV, ribavirin.

* Those sustained virologic responders with paired biopsies (pre- and post- treatment).

† Months between pre- and post-post treatment biopsy.

‡ Ninety-eight percent of biopsies.

§ Advanced fibrosis or cirrhosis on baseline liver biopsy.

‖ Median biopsy length.

frequent in sustained virologic responders relative to nonresponders or compared with those untreated (Table 3); however, most data are derived from uncontrolled, largely retrospective analyses with relatively short follow-up periods, compared with the protracted natural history of HCV infection. Because studies were not randomized, prognostic factors, such as alcohol use or even coffee consumption [80], might have contributed to differences between sustained responders and nonresponders. In some studies, variables that affect clinical event frequency, such as serum bilirubin [81], were disparate between nonresponders and SVR achievers. Furthermore, selection bias was likely present, because some cirrhotic patients were probably considered to be too ill for treatment and were excluded from these analyses.

Nonetheless, persons with SVR seem to have an excellent prognosis, as shown in 2 recent meta-analyses involving patients with HCV infection who were treated with interferon-based therapies. In the first analysis of >5000 SVR-achieving patients in 26 studies, compared to patients with advanced fibrosis who failed therapy (pooled decompensation rate, 2.92%/year; 95% CI, 1.61–4.22), SVR-achieving patients had a much lower relative risk of liver decompensation (relative risk [RR], 0.013; 95% CI, .06–.27) [82]. In another analysis of 286 persons with SVR from 8 European studies, the decompensation rate after 5 years of follow-up was 1% (95% CI, 0.0%–2.3%) [13]. These low decompensation rates compare very favorably to the 5-year 18%–25% decompensating events in natural history studies involving compensated HCV-infected cirrhotic patients [83–85]. More noteworthy, in the European analysis, 5-year survival among patients achieving SVR was comparable to that of the general population (standard mortality ratio, 1.4; 95% CI, 0.3–2.5) [13].

Table 3. Clinical Benefits of Sustained Virologic Responders (SR) to Interferon-Based Therapy

Analysis type	Number of sustained responders	Therapy	Follow-up interval (years)	Clinical events	Reference
Randomized, controlled trial	15*	PEG, PEG/RBV	3.2 (median)	NR vs. SR: 38.3% vs. 6.2%; HCC, decomp, hep-death, $P = .03$ by log rank test; SR: 32% absolute risk reduction	DiMarco et al 2007 [61]
Retrospective cohort	80	IFN, IFN/RBV, PEG/RBV	5–7	NR vs. SR: HCC, decomp, hep-death, aHR = 11.7, (95% CI 1.25–110), *P* values not reported	Pradat et al 2007 [14]
Retrospective cohort	37*	IFN, IFN/RBV, PEG, PEG/RBV	7.7 (mean)	NR vs. SR: 44.7% vs. 8.1%, HCC, decomp, hep-death, HR = 6.3, (95% CI 1.9–20.4), $P = .002$	Braks et al 2007 [62]
Retrospective cohort	142*	IFN, IFN/RBV, PEG, PEG/RBV	2.1 (mean)	SR vs. NR: Any event HR = .20 (95% CI, .07–.55), $P = .003$; P = ns for HCC and hep-death, separately	Veldt et al 2007 [63]
Retrospective cohort	124*	IFN	8.0 (mean)	NR vs. SR: HCC, aHR = 2.59, (95% CI, 1.13–5.97), $P = .025$; hep-death, aHR = 6.97, (95% CI, 1.71–28.42), $P = .007$	Bruno et al 2007 [64]
Prospective cohort	140†	IFN, IFN-beta, IFN/RBV	7.4 (mean)	SR vs. NR: HCC, HR = .193 (95% CI, .083–.45), $P < .0001$; hep-death, HR = .13 (95%0.03–.59), $P = .007$; overall mortality, HR = .39 (.16–.93), $P = .034$	Arase et al 2007 [65]
Retrospective cohort	57	IFN, IFN/RBV	3.4 (median)	SR vs. NR: HCC, 0% vs. 3.7%; decomp, 0% vs. 2.5%; *P* values not reported	Kim et al 2006 [66]
Prospective cohort	64	IFN	6.8 (mean)	SR vs. NT: HCC, aHR = .31 (95% CI, .16–.61), $P < .001$; overall survival, aHR = .05 (95% CI, .0006–.34), $P = .003$	Shiratori et al 2005 [67]
Retrospective cohort	50	IFN	9.1 (median)	SR vs. NR: HCC, 2% vs. 11%, $P = .007$; decomp, 2% vs. 25%, $P < .001$; hep-death or xplant, 2% vs. 15%, $P = .003$. All univariate analysis; whereas, P = ns in multivariate analysis when controlling for liver fibrosis and serum albumin	Coverdale et al 2004 [68]
Retrospective cohort	116	IFN, IFN-beta	8.3 (mean)	SR vs. NT: hep-death, HR = .30 (95% CI, .003–.267), $P = .0017$; overall survival, HR = .219 (95% CI, .068–.710), $P = .0144$	Imazeki et al 2003 [69]
Retrosective and prospective cohort‡	817	IFN, IFN-beta	5.4 (mean)	SR vs. NT: hep-death, HR = .05 (95% CI, .012–.216), $P = .0001$	Yoshida et al 2002 [70]
Retrospective cohort	789	IFN, IFN-beta	4.3 (mean)	SR vs. NT: HCC, aHR = .197 (95% CI, .099–.392), $P < .001$	Yoshida et al 1999 [71]

Table 3. (*Continued*)

Analysis type	Number of sustained responders	Therapy	Follow-up interval (years)	Clinical events	Reference
Retrospective cohort	152	IFN	11.3 (mean)	SR vs. NR: HCC, 2.2% vs. 26%, $P < .0001$; hep-death, 0% vs. 16.3%, $P < .0001$	Akuta et al 2005 [72]
Retrospective cohort	73	IFN	3.1 (mean)	NR vs. SR: HCC, HR = 3.521 (95% CI, 1.087–11.36), $P = .036$	Hung et al 2006 [73]
Retrospective cohort	48*	IFN, IFN-beta	4.6 (median)	SR vs. NR: HCC, HR = .185 (95% CI, .042–.810), $P = .025$	Hasegawa et al 2007 [74]
Retrospective-prospective cohort	715	IFN, IFN/RBV	5.2 (mean)	SR vs. NT: HCC, HR = .245 (95% CI, .130–.463), $P < .0001$; overall mortality, HR = .370 (95% CI, .138–.986), $P = .047$	Yu et al 2006 [75]
Prospective cohort	28	IFN, PEG/RBV	14.4 (median)	Events per 100 person-years for SR, NR, NT: HCC, 1.9, 2.8, 2.9, P = ns between SR and NR; decomp, .3, 3.8, 3.5, $P = .003$ between SR and NR or NT; hep-death, 1.0, 2.4, 3.0, $P = .03$ between SR and NR or NT	Bruno et al 2009 [76]
Prospective cohort	140*	PEG/RBV	86 (median)	SR vs. NR: HCC, HR = .19 (95% CI, .04–.8), decomp and hep-death, HR = .15 (95% CI, .06–.38)	Morgan et al 2010 [77]
Retrospective-prospective cohort	307	IFN, IFN/RBV, PEG, PEG/RBV	3.5 (median)	NR vs. SR: HCC, aHR = 3.06 (95% CI, 1.12–8.39), $P = .029$; decomp, aHR = 4.73 (95% CI, 1.09–20.57), $P = 0.038$; hep-death, aHR = 3.71(95% CI, 1.05–13.05), $P = .041$	Cardoso et al 2010 [78]
Retrospective Cohort	7,420	PEG/RBV	3.7 (mean)	SR vs. NR: overall mortality, G1 aHR = .67(95%CI, .56–.79), $P = <.0001$; G2 aHR = .63(95%CI, .45–.86), $P = .004$; G3 aHR=.45(95%CI, .32–.65), $P < .0001$	Backus et al 2010 [79]

Abbreviations. aHR, adjusted hazard ratio; decomp, decompensating liver events (eg, variceal bleeding); G, viral genotype; HCC, hepatocellular carcinoma; hep-death, liver-related mortality; HR, hazard ratio; IFN, standard interferon alpha; NR, nonresponders; ns, not significant; NT, not treated; PEG, pegylated interferon; RBV, ribavirin; xplant, orthotopic liver transplantation.

* All patients with advanced fibrosis or cirrhosis on baseline liver biopsy.

† All patients older than 60 years.

‡ Prospective analysis after 1994.

New, preliminary evidence from a large Veterans' Affairs study demonstrated that SVR may improve all-cause mortality, not just that related to the liver [79]. The cohort of 16,864 HCV-infected patients had high rates of comorbidities that impact survival, such as chronic obstructive pulmonary disease, tobacco use, and diabetes. All were treated with pegylated interferon with ribavirin, and the overall SVR rate was 44% (all genotypes). In both unadjusted and in multivariate models controlling for factors, such as age, body mass index, and comorbidities, SVR independently and significantly reduced overall mortality, irrespective of viral genotype (Table 3). Limitations of this analysis were its observational data (not randomized to SVR versus no SVR) and its reliance on *International Classification of Diseases, Ninth Revision* codes for patient diagnoses.

Finally, clinical outcomes may also be diminished in SVR-achieving HIV-coinfected patients [86], in liver transplant

recipients [87], and even in decompensated cirrhotics who are able to tolerate therapy [88].

Aside from preventing variceal bleeding and other decompensating events, achieving SVR in compensated cirrhotics may also prevent the development of esophageal varices de novo [89]. Much of the morbidity associated with advanced liver disease, such as esophageal varices development, is related to portal hypertension. The mechanism by which SVR can diminish liver-related complications may be the lowering of portal pressure. In a small study involving HCV-infected cirrhotics, 21% of whom achieved SVR with pegylated interferon with ribavirin therapy, sustained responders had a significant reduction in portal pressure as measured by hepatic vein pressure gradient (HVPG) relative to nonresponders; among portal hypertensives, more sustained responders achieved a 20% reduction in HVPG level relative to that of nonresponders (71% vs 20%; $P = .01$) [90]. In the aforementioned study of compensated cirrhotics for whom reaching SVR may have prevented esophageal varices, 4 of 4 SVR-achieving patients whose HVPGs were measured experienced post-SVR decrements <10 mm Hg [89], a threshold 2 mm Hg below which is thought to be protective against varices development [91].

Among the most dire consequences of cirrhosis is HCC, for which the median survival is only 8 months [92]. Three large meta-analyses (2178–4614 patients) have shown that HCC development is lessened in persons with SVR relative to untreated patients (risk reduction, 19.1%; 95% CI, 13.1–25.2%; $P < .001$) [93] and in sustained virologic responders relative to nonresponders (OR, .35; 95% CI, .26- –.46; $P < .001$) [94]. In the third analysis, non-responders had a higher HCC incidence compared with that in sustained responders (OR:3.7, 95% CI, 1.7–7.8) [95].

Recently described murine models suggest ways in which SVR could decrease HCC development. The cytokines lymphotoxin (LT) α and β (members of the TNF superfamily) and their receptor (LTβR) are dramatically upregulated in HCV-induced hepatitis and HCC. In this environment of activated immune cells producing cytotoxic cytokines, hepatocytes are susceptible to chromosomal derangements leading to HCC. Past studies have shown that chronic inflammatory stimuli promote hepatic carcinogenesis [96, 97]. In this recent study [98], the authors inhibited LTβR in LT-transgenic mice with hepatitis, which led to diminished development of HCC. Perhaps, if the inflammatory microenvironment could be attenuated by viral eradication (SVR), this might, in turn, lessen HCC occurrence. In another murine model, platelet-derived growth factor C induced extensive fibrosis and HCC development [99].

Apparently, HCC risk is diminished but not eliminated with viral clearance, because several authors have noted HCC development despite patients' achieving SVR [10, 47, 52, 68, 77, 100–107]. Independent factors for post-SVR HCC include age, male sex, alcohol consumption, and more advanced pretreatment fibrosis [108, 109]. Thus, cirrhotic patients achieving SVR should still receive HCC surveillance, as reflected in current guidelines [110].

Insulin Resistance and Diabetes Mellitus. Chronic HCV infection has been linked to metabolic sequelae, such as insulin resistance (IR), and type 2 diabetes mellitus (T2DM). Data from an animal model suggest that HCV directly induces IR [111]. In human studies in HCV-infected patients, IR, measured by the homeostasis model assessment of IR (HOMA-IR), is associated with fibrosis progression [112, 113] and diminished SVR rates [114, 115]. Epidemiologic data reveal an association between HCV infection and an increased incidence and prevalence of T2DM [116–118]. If HCV causes IR in humans, viral eradication or SVR should improve insulin sensitivity.

The effect of SVR on insulin resistance was first demonstrated in 50 non-diabetic patients treated with peginterferon and ribavirin [114]. In sustained responders, IR (HOMA-IR) decreased significantly by the end of follow-up, compared with pretreatment (mean ± SD, 2.55 ± 2.52 vs 1.50 ± 0.77; $P < .05$), but nonresponders experienced no significant change in IR (mean ± SD, 3.65 ± 2.03 to 3.53 ± 1.85; the P value was not statistically significant). This small study was limited by failing to adjust for baseline differences in HOMA-IR and fibrosis, when comparing sustained responders with nonresponders.

Data from 96 patients in the HALT-C study corroborate that HCV suppression correlates with IR improvement. Measuring HOMA2-IR (an updated insulin resistance model) at baseline and at week 20 and adjusting only for baseline HOMA2-IR, investigators found mean HOMA2-IR differences of −2.23 for complete responders, −0.90 for partial responders, and +0.18 for nonresponders ($P = .036$). HOMA2-IR improvement with HCV clearance was independent of potential confounders, including age, body mass index, sex, infection duration, and fibrosis [119]. Examining a subset of 127 HCV-infected patients with baseline IR in a treatment trial, Conjeevaram et al [120] found that only SVR-achieving patients had significant decreases in HOMA2-IR during and after therapy. Improvement in IR persisted even after patients regained weight following treatment.

The aforementioned studies used surrogate estimates of IR and, therefore, provide only indirect evidence that HCV affects IR.

Firm evidence supports the conclusion that achievement of SVR reduces the risk of impaired fasting glucose and even overt T2DM development. Simó et al [121] studied 234 patients with chronic HCV infection after treatment. Over a mean follow-up period of 5.7 years, 14.6% of SVR-achieving patients and 34.1% of non-responders developed glucose abnormalities (P=.001). After adjustment for recognized predictors of T2DM, the hazard ratio for glucose abnormalities among patients with SVR was

0.48 (95% CI, .24–.98; $P = .04$). Romero-Gómez et al [122], in a similar study, identified 2 independent variables associated with alterations in glucose metabolism: fibrosis stage (OR, 1.46; 95% CI, 1.06–2.01; $P = .02$) and SVR (OR, 0.44; 95% CI, .20–.97; $P = .04$). Achievement of SVR decreased the incidence of T2DM and impaired fasting glucose by half during posttreatment follow-up. Arase et al [123] observed a cohort of 2842 patients treated for HCV infection over a mean period of 6.4 years, assessing for T2DM development. T2DM development was associated with age ⩾50 years, baseline impaired fasting glucose, advanced fibrosis on biopsy, and HCV persistence. SVR attainment led to a two-thirds reduction in T2DM risk after therapy.

Mounting evidence suggests that SVR decreases IR in HCV-infected patients. This appears to translate into clinical benefits, because achievement of SVR reduces the risk of impaired fasting glucose and T2DM development.

SVR in the Era of Directly Acting Antiviral Therapy

For HCV-monoinfected patients with genotype 1 infection (the most common US isolate), the current standard of care, pegylated interferon with ribavirin, yields relatively low SVR rates (42%–46%) [8, 9]. Clearly, additional effective therapies are warranted. Insights into HCV virology have identified viral targets for potential novel therapeutics. This new approach to HCV therapy uses a direct antiviral mechanism and has been deemed directly acting antiviral therapy (DAA). The HCV NS3 protein, in addition to its cofactor NS4A, form a serine protease that cleaves the posttranslational HCV polyprotein into 4 nonstructural proteins. One of these proteins is NS5B, which encodes the HCV RNA polymerase. Furthest along in DAA development are 2 NS3/4A protease inhibitors that have recently completed phase 3 trials and may be approved this year in combination with pegylated interferon with ribavirin. SVR rates for genotype 1–infected treatment-naive monoinfected patients are as high as 66%–75% with triple combination therapy [124, 125].

The hope that DAAs might readily replace pegylated interferon was dashed with the realization that DAA monotherapy selects for resistance mutations rapidly [126–128]. Nevertheless, the NS3/4A protease inhibitor telaprevir monotherapy without interferon has been shown to effect SVR [129]. A more realistic treatment strategy to avoid the selection of viral breakthrough and resistant variants is to use DAAs in combination without interferon with ribavirin.

The Interferon-Free Regimen for the Management of HCV trial used 14-day regimens of the NS3/4A protease inhibitor R7227 (danopevir) and the NS5B polymerase inhibitor (RG7128) in genotype 1–infected patients. At the highest doses tested in treatment-naive patients, no breakthrough resistance was observed, and 5 of 8 patients had undetectable viremia at day 14 [130]. Because these patients were then switched to pegylated interferon with ribavirin, the ultimate efficacy (SVR) from the interferon-sparing portion of the regimen will not be elucidated. However, using a combination of another protease and polymerase inhibitor (telaprevir and MS-0608, respectively) for 4 weeks, investigators successfully eradicated HCV from human hepatocyte chimeric mice followed up to 20 weeks posttherapy [131, 132]. Several trials are underway with 2 DAAs, in combination without any interferon or ribavirin in humans.

To raise an effective barrier to resistance emergence and to ultimately achieve SVR without interferon, >2 DAAs may be required. Compensatory mutations occur within days of drug exposure because of the drugs' selective pressure. It is estimated that, for a regimen composed of only DAAs, a barrier of ⩾4 mutations is likely to be required to prevent resistance-induced loss of virologic control and, thus, engender SVR [133].

In a follow-up period of up to 48 weeks after SVR achievement with pegylated interferon with ribavirin and a protease inhibitor in phase 2 trials, no cases of late relapse had yet occurred [134, 135]. Nonetheless, long-term prospective data will be needed to confirm equivalence to SVR with the current standard of care. It is hoped that all the aforementioned benefits of SVR will be better championed by DAAs in the pipeline that will improve SVR rates among patients, particularly those who heretofore had been deemed as difficult to treat.

Table 4. Summary of Potential Benefits of Sustained Virologic Response

Endpoint	Potential benefit of SVR	Limitations of data
Longevity of Response	Rate of late relapse extremely low (<1%)	Subject, follow-up, laboratory assay and therapy heterogeneity
Histology	Compared to pre-treatment liver biopsies, improved inflammation and fibrosis	Sampling error Interobserver variability Untreated patients can likewise show improvement
Clinical Events and Survival	Compared to non-responders, less frequent hepatic complications, liver-related mortality and incidence of HCC	Mostly uncontrolled, non-randomized, retrospective analyses with short-term follow-up Selection bias
Insulin Resistance	Compared to non-responders, less insulin resistance and diminished development of impaired fasting glucose and diabetes	Small sample size (some insulin resistance studies) Uncontrolled baseline factors in some analyses

Abbreviations. HCC, hepatocellular carcinoma; SVR, sustained virologic response.

CONCLUSION

In chronic HCV infection, therapy-induced SVR is a clinically meaningful end point (Table 4). SVR is a durable marker of viral eradication, because evidence for extrahepatic residual viremia is limited, and multiple reports demonstrate that late relapse is rarely observed; SVR is tantamount to cure. Besides posttherapy improvement in hepatic histologic damage, it is likely that SVR-achieving patients have a diminution in HCV-related insulin resistance and in diabetes development and, relative to therapy nonresponders, have a striking reduction in liver-related complications and mortality.

With the anticipated approval of DAAs to be used in concert with interferon-based therapy, it is reassuring that SVR rates achieved with triple therapy (eg, HCV protease inhibitor plus pegylated interferon with ribavirin) will be superior to those with current standard of care and SVR may be equally durable.

In conclusion, SVR should no longer be considered to be a surrogate end point, but a clinically meaningful end point of successful therapy for hepatitis C infection; SVR represents a cure and so much more.

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