Goals for Treatment and Predicting Response

This is a PDF version of the following document:
Module 4: Evaluation and Preparation for Hepatitis C Treatment
Lesson 1: Goals for Treatment and Predicting Response

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Goals and Rationale for Treatment

Sustained Virologic Response (SVR)

A sustained virologic response (SVR) is an undetectable HCV RNA level using a sensitive assay (typically with a lower limit of 25 IU/ml) 12 weeks after completion of therapy for hepatitis C (Figure 1). This is typically referred to as the SVR12 and achieving an SVR12 is the goal of therapy.[1] Among persons who achieve an SVR12, more than 99% go on to achieve an SVR24.[2] Trial outcomes with SVR time frames of shorter duration (SVR8, and SVR4) have been presented in an effort to expedite conclusions from these trials, but SVR4 and SVR8 are not the standard in clinical practice.

Durability of SVR

Long-term follow-up of patients who achieve an SVR24 has shown that nearly 100% remain HCV RNA negative years after therapy.[3,4,5] The largest studies have shown a minimal relapse rate, between 0 to 1%.[6] Thus, an undetectable HCV RNA 24 weeks after antiviral therapy can be considered a virologic cure.

Impact of SVR on Liver Histology

Patients who achieve an SVR are more likely to have an improvement in liver inflammation and fibrosis than those who do not achieve an SVR. In a pooled analysis of patients who had paired liver biopsies before and 1 months to 6 years after treatment with standard interferon monotherapy, peginterferon monotherapy, or peginterferon with ribavirin, those patients who had an SVR were twice as likely to have lower necroinflammatory scores after treatment, compared to patients who relapsed (67% versus 32%).[7] In the same study, improvement in baseline scores were more likely to occur in those who had longer periods of undetectable HCV RNA. In some cases, there was complete regression of liver fibrosis. Multiple studies have confirmed this long-term histologic benefit.[3,4,5,8]

Impact of SVR on Survival and Natural History

Clearance of HCV RNA with treatment has been shown to have a beneficial impact on a variety of clinical outcomes, both liver and non-liver related [Pearlman, Mira, Kutala, Dieperick].[6,9,10,11] One study demonstrated that U.S. veterans with chronic hepatitis C with age-matched controls without hepatitis C, investigators demonstrated that hepatitis C infection increased the risk of death by approximately 37%. However, veterans with chronic hepatitis C infection who received at least 48 weeks of peginterferon and ribavirin had a 60% reduction in mortality compared with untreated veterans (Figure 2).[12] In a study involving the general population, patients with advanced fibrosis

who underwent antiviral therapy and achieved an SVR had reduction in overall mortality, liver-related death, liver failure, and hepatocellular carcinoma when compared with those who did not achieve an SVR (Figure 3).[13] Most of this survival benefit appeared to result from the marked reduction in liver failure, but a number of studies have also demonstrated the benefit of an SVR to all-cause mortality[14,15] and non-liver-related deaths.[16] In a recent meta-analysis of 35 studies, investigators showed a clear benefit in 5-year overall survival with HCV treatment, including patients with cirrhosis and with HIV coinfection (Figure 4).[17]

Impact of SVR on Other Medical Conditions

Hepatitis C can cause a myriad of extrahepatic complications, including membranoproliferative glomerulonephritis and Non Hodgkin's lymphoma. Chronic hepatitis C infection is associated with a higher prevalence of insulin resistance and diabetes mellitus. In some patients, successful treatment of hepatitis C is associated with improvement or remission of these underlying conditions.[18,19] In addition, achieving an SVR has been shown to reduce the chance of impaired fasting glucose and diabetes development by 50%, an effect that is independent of other established risk factors for diabetes, such as age and body mass index.

Viral Factors that Predict Response to Therapy

HCV Genotype

Hepatitis C is classified into 6 major genotypes, numbered 1 through 6. In the prior interferon era of treatment, genotype was the strongest predictor of obtaining an SVR.[20,21,22] In the current direct-acting antiviral (DAA) era, the role of HCV genotype in predicting treatment response has decreased significantly given the high efficacy of different DAA combinations across all genotypes and the introduction of pan-genotypic agents.

HCV RNA Level

In the registration clinical trials of peginterferon and ribavirin, a baseline HCV RNA level over 2 million IU/ml was associated with a 9% lower chance of cure.[20] Subsequent studies found that patients with high HCV RNA levels and genotype 1 infection had a 16 to 27% lower chance of achieving an SVR depending on the cut-off used.[23] In the current DAA era, the baseline HCV RNA appears to have little impact on the likelihood of achieving an SVR. A very high baseline viral level (> 6 million IU/ml) however has been shown in post-hoc analysis to be associated with reduced likelihood of SVR with shorter duration (8 weeks) of therapy with ledipasvir-sofosbuvir.[24]

Host Factors that Predict Response to Therapy

Race

African-American patients with hepatitis C have historically had poorer responses to interferon-based therapy, as shown in a comparative analysis of responses to treatment with peginterferon and ribavirin in persons with genotype 1 infection (SVR rate in African-Americans was 19% versus 52% in Caucasians.[25] Latinos with genotype 1 treated with peginterferon and ribavirin also have had reduced SVR rates compared with Caucasians (34% versus 49%).[26] Most registration studies of all-oral DAA combination therapy have not demonstrated significant differences in SVR by race,[27] although there may not have been sufficient power to detect a difference if one existed. An observational study of DAA effectiveness in over 17,000 US veterans did suggest a slightly reduced likelihood of SVR in black patients (adjusted odds ratio of 0.8, p-value=0.004).[28]

IL28B Genotype

The difference in response rates between African-Americans and Caucasians is largely explained by genetic differences in the IL28B gene region on chromosome 19. This region encodes for the host production of interferon-lambda. The majority of African-Americans have either the less favorable genotypes (CT or TT). In the interferon era, the CT or TT genotype was associated with a 40% lower SVR rate compared to patients with the CC allele (Figure 5).[29] Asians have the highest proportion of the CC genotype, which may explain their better response to interferon-based therapy. The IL28B genotype does not appear to influence treatment response to interferon-free combination DAA therapy.

Age

In a multivariate model of predictors for response to interferon and ribavirin, increasing age was significantly associated with a lower chance of cure. In the modern DAA era, age does not significantly influence treatment response.

Gender

Gender is not an independent predictor of antiviral response in patients with chronic hepatitis C infection.

Degree of Hepatic Fibrosis

Advanced fibrosis is typically defined as F3 (pre-cirrhosis or bridging fibrosis) and F4 (cirrhosis) on liver biopsy. In the registration trials of peginterferon, advanced fibrosis was associated with a 10 to 20% lower cure rate, across all genotypes.[20,21,22] This lower SVR rate among patients with cirrhosis has persisted to a lesser extent in the DAA era,[28,30] with differences that are more pronounced in patients with greater liver disease severity. Patients with decompensated cirrhosis (Child-Pugh class B or C) had SVR rates of 86-87% with 12 weeks of ledipasvir-sofosbuvir compared with SVR rates of greater than 95% in similarly treated non-cirrhotic patients.[31]

Prior Treatment Response

Type of Treatment Response with Prior FailurE

A history of prior treatment failure had a significant influence on the probability of response to treatment with peginterferon and ribavirin plus a protease inhibitor (telaprevir or boceprevir).[23,32,33] Prior treatment failure with peginterferon and ribavirin, however, does not appear to have the same impact on treatment response in the DAA era, particularly in non-cirrhotic patients. In general, when using new recommended DAA-based therapy, more than 90% of previously treated patients should achieve an SVR with retreatment. The one exception is treatment-experienced cirrhotic patients who may be slightly more refractory to combination DAA therapy depending on the HCV genotype and the specific agents used for therapy. The addition of ribavirin or extension of therapy duration has been proposed to minimize these differences in SVR.[34]

Summary Points

- The goal of antiviral therapy for hepatitis C is a sustained virologic response, defined as a negative HCV RNA level 12 weeks after stopping antivirals; the SVR12 has a high correlation with SVR24.
- An SVR is durable, is associated with reversal of hepatic inflammation and fibrosis, and can reduce the chance of dying from hepatitis C by at least 60%.
- In the interferon era, HCV genotype was a strong predictor of achieving an SVR. In the current DAA era, the genotype has a reduced role in predicting treatment response given the availability of a variety of DAA combinations with high efficacy across genotypes.
- African-Americans historically responded at lower rates to peginterferon and ribavirin when compared with Caucasians, a difference largely attributable to genetic differences at the IL28B gene locus. In contrast, most studies of all-oral DAA combination therapy have not demonstrated significant differences in SVR by race.
- Patients with more advanced fibrosis may have lower response rates to standard 12-week DAA treatment than those with less advanced fibrosis, particularly when this involves patients with decompensated cirrhosis. Strategies to improve treatment responses in patients with cirrhosis have included the addition of ribavirin to the regimen and/or lengthening the duration of therapy.

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Figures

Figure 1 Sustained Virologic Response 12 (SVR 12)

This graphic shows an example of an SVR12 in a patient who received 12 weeks of HCV treatment. The SVR12 is shown by the undetectable HCV RNA12 weeks after treatment was stopped.

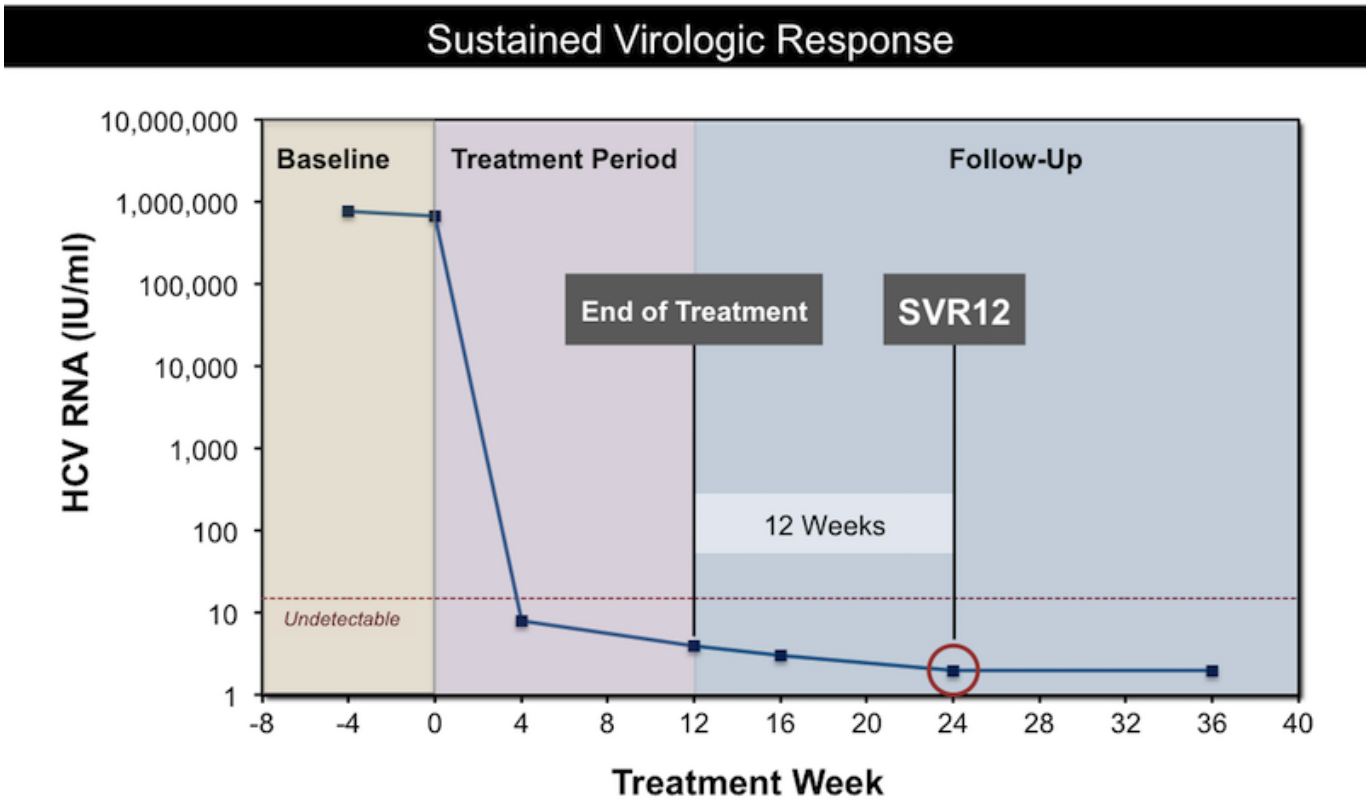


Figure 2 Correlation of Relative Risk of Death and Duration of HCV Therapy

Investigators used a national sample of HCV-infected veterans and HCV-uninfected controls to examine the effect of HCV treatment on survival. This graphic illustrates longer treatment duration correlated with improved survival.

Source: Butt AA, Wang X, Moore CG. Effect of hepatitis C virus and its treatment on survival. Hepatology. 2009;50:387-92.

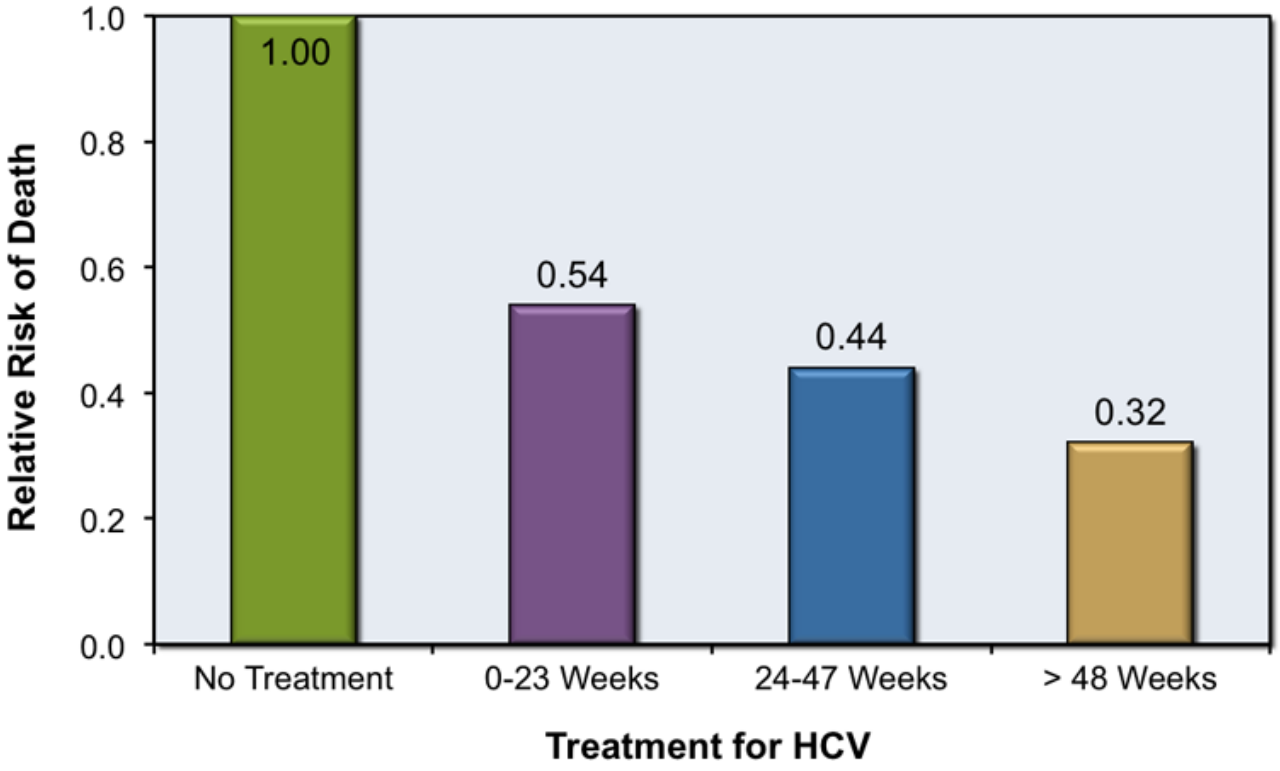


Figure 3 Clinical Outcome by Response to Treatment in Patients with Chronic Hepatitis C and Advanced Fibrosis

This retrospective study was performed in Europe and Canada and examined whether sustained virologic response following hepatitis C treatment correlated with clinical outcomes. The major finding was that treatment was associated with improved clinical outcomes, primarily because of lower rates of liver failure.

Source: Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med. 2007;147:677-84.

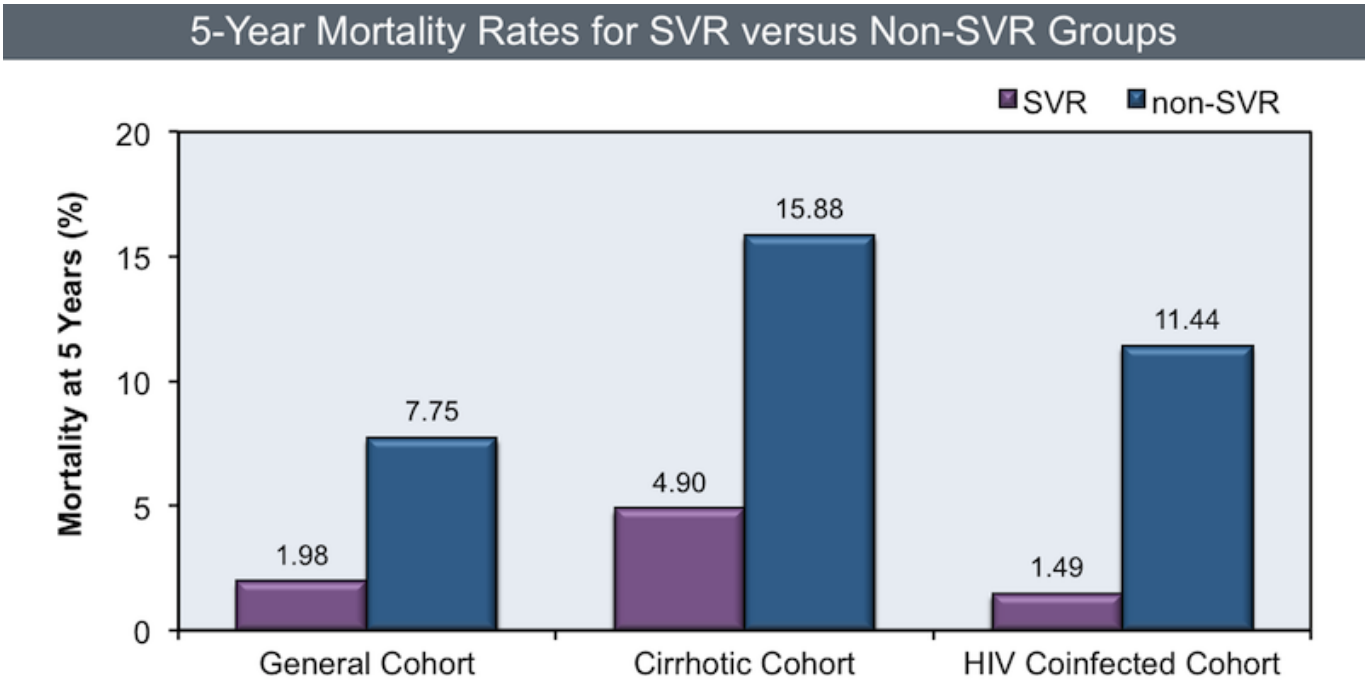
Clinical Outcomes by Response to Hepatitis C Treatment

Outcome	Patients with SVR	Patients without SVR	Hazard Ratio
	Events per 10,000 Patient-Years		
Overall Death	71	193	0.44
Liver Related Death	36	283	0.14
Non-Liver Related Death	36	40	1.21
Liver Failure	0	365	0.03
Hepatocellular Carcinoma	107	277	0.46

Figure 4 5-Year Survival Rate following HCV Treatment Based on SVR Response

This graphic is based on data from 31 studies published from 2000 to 2014, including a total of 33,360 patients. The 5-year mortality rates shown are based on whether the patient achieved an SVR.

Source: Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-analysis of the Survival Benefit of Achieving a Sustained Virological Response. Clin Infect Dis. 2015;61:730-40.



Abbreviations: SVR= sustained virologic response

Figure 5 Correlation of IL28B Genotype and Response to Hepatitis C Therapy

Patients with genotype 1 hepatitis C received treatment with 48 weeks of peginterferon and ribavirin. This graphic showed the response to therapy based on IL28B genotype (T/T, T/C, C/C) and based on the patient's ethnicity. Patients with CC genotype have higher SVR rates regardless of ethnicity. A lower percentage of African Americans have CC genotype, which correlates with lower overall response to therapy.

Source: Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009;461:399-401.