# Predicting the probable outcome of treatment in HCV patients

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***Abstract*:** Hepatitis C virus (HCV) is a major cause of chronic liver disease infecting more than 170 million people worldwide. HCV produces a wide gamut of manifestations varying from mild self-limiting disease to cirrhosis and hepatocellular carcinoma. A variety of viral, environmental and host genetic factors contribute to the clinical spectrum of patients infected with HCV and influence response to interferon (IFN) therapy. Predicting the probable outcome of treatment in patients with HCV infection has always been a challenging task. Treatment of HCV by pegylated interferon (peg-IFN) plus ribavirin eradicates the virus in approximately 60% of patients – HCV genotype 1 (42–51% response rates) and genotypes 2 and 3 (76–84% response rates); however, a significant number of patients do not respond to therapy or relapse following discontinuation of treatment or have significant side effects that preclude further treatment. Accurately predicting the patients who will respond to therapy is becoming increasingly important, both from the point of patient care and also with respect to the healthcare cost as clinicians need to continue treatment in patients who will respond and stop treatment in patients who are unlikely to respond. Viral RNA measurements and genotyping are used to optimize treatment as a low viral load and nongenotype 1 is more likely to be associated with sustained virological response (SVR). Rapid virological response (RVR) defined by undetectable HCV RNA at 4 weeks of treatment is increasingly being recognized as a powerful tool for predicting treatment response. A variety of host factors including single nuclear polymorphisms (SNPs) of IFN response genes, insulin resistance, obesity, ethnicity, human leukocyte antigens and difference in T-cell immune response has been found to modulate the response to antiviral treatment. The presence of severe fibrosis/cirrhosis on pretreatment liver biopsy predicts a poor response to treatment. Recent studies on gene expression profiling and characterization of the liver and serum proteome provide options to accurately predict the outcome of patients infected with HCV in the future. Future studies on the factors that predict treatment response and tailoring treatment based on this is required if we are to conquer this disease.

***Keywords*:** hepatitis C, pegylated interferon, ribavirin, predicting outcome, sustained virological response

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## Introduction

Hepatitis C virus (HCV) is a major cause of chronic liver disease affecting close to 170 million people worldwide including three million people infected in the US (1.3% of the US population) and five million in Western Europe [Armstrong *et al.* 2006; National Institutes of Health, 2002; Wong *et al.* 2000; European Association for the Study of the Liver 1999]. HCV is an enveloped flavivirus with a 9.6 kb single-stranded RNA genome [Choo *et al.* 1989]. Approximately 85% of patients acutely infected with HCV progress to chronic liver disease with persistence of HCV RNA for more than 6 months [National Institutes of Health, 2002]. The incidence of new HCV infections has decreased over the years; however, the individuals previously affected with HCV who have now progressed to chronic HCV infection are generating increasing expenditure of healthcare costs worldwide. In fact, in an analysis of cost of HCV treatment, the total direct healthcare cost associated with HCV was estimated to be more than $1 billion in 1998. Also the estimated cost for outpatient

services was projected to be $24 million and close to $530 million was spent on antiviral treatment of HCV. Also, the projections are for a four-fold increase in the burden of chronic HCV infection between 1990 and 2015 [Kim, 2002].

Among patients with chronic HCV infection, 15–20% progress to end-stage liver disease [Liang *et al.* 2000] and approximately 1–4% of these will develop hepatocellular carcinoma. Also, the prevalence of infection is highest among middle-aged patients and more of these patients will progress to cirrhosis or hepatocellular carcinoma with time [Armstrong *et al.* 2006]. With hepatitis C being a major health care concern, predicting the outcome of treatment in these patients becomes all the more important [Centers for Disease Control and Prevention, 2005].

Eradication of HCV by antiviral treatment improves liver histology and patient survival [Niederau *et al.* 1998; Marcellin *et al.* 1997]. Sustained virologic response (SVR) defined by undetectable serum HCV RNA 6 months after treatment is completed, is the goal of treatment as patients who achieve SVR with treatment have less than 5% chance of recurrence of the disease [Shiffman, 2006] The rates of SVR have increased with improvements in antiviral therapy. SVR rates with interferon (IFN) monotherapy was approximately 6–12%, increasing to 38–42% with conventional IFN and ribavirin (RBV), and increasing to as high as 63% with pegylated IFN (peg-IFN) and RBV [Fried *et al.* 2002; Manns *et al.* 2001; McHutchison *et al.* 1998; Poynard *et al.* 1995].

Unfortunately, the use of peg-IFN and RBV is associated with adverse effects in a significant number of patients necessitating either discontinuation of the drug or dose reductions. Early detection of nonresponders and continuing treatment for patients who are more likely to respond is of major importance in improving the outcome of patients with chronic HCV infection. Hence, accurate prediction of treatment response has become a major factor in the management algorithm for chronic HCV infection.

Over the last two decades, several genetic, patient and viral-related factors have been identified which predict the varying outcome of patients infected with hepatitis C and can modulate the patient's response to treatment. This review article addresses the present understanding of the factors which predict the varying outcome of patients infected with hepatitis C and the future management implications of this variable response to hepatitis C infection.

## Review criteria

In January 2009, we searched MEDLINE from 1990 to the present using the medical subject headings terms: 'chronic hepatitis C', 'chronic hepatitis C and treatment response', 'chronic hepatitis C and sustained virological response', 'chronic hepatitis C and relapse/non response', 'chronic hepatitis C and genotype' and the keyword 'chronic hepatitis C'. Full papers and abstracts without language restrictions were considered.

## Various treatment outcomes in HCV patients

SVR defined by undetectable serum HCV RNA 6 months after treatment is completed is the goal of treatment, as patients who achieve SVR with treatment have less than 5% chance of recurrence of the disease [Shiffman, 2006]. However, recent studies have shown that early assessment and close monitoring of viral kinetics can more accurately predict outcome and could allow us to optimize the treatment based on individual patient kinetics. Early virologic response (EVR) is defined as a $\geq$2-$\log_{10}$ decrease in the HCV RNA level or as an undetectable HCV RNA level by 12 weeks of therapy [Dienstag and McHutchison, 2006; Strader *et al.* 2004] and is considered an important predictor of treatment outcome, because patients who do not achieve EVR by 12 weeks have a 97–100% for not achieving SVR in the future [Ferenci *et al.* 2005; Davis *et al.* 2003]. Thus, the high negative predictive value helps in patient management. Rapid virologic response (RVR), defined as an undetectable serum HCV RNA level at week 4 of treatment, is an emerging tool in improving individualized patient care; it offers an even earlier opportunity to consider truncated treatment.

Nonresponse is defined by <2 log decrease in baseline HCV RNA levels after 12 weeks of therapy, while partial response is defined by >2 log decline in HCV RNA levels in 12 weeks, but the virus persists after 24 weeks of treatment [Shiffman, 2006]. Table 1 summarizes the various treatment outcomes.

These varied treatment outcomes in the treatment of HCV infection is baffling. Understanding the probable outcome of treatment either before

**Table 1.** Endpoint of treatment outcomes of hepatitis C virus (HCV) infection.

| Treatment outcome | Definition |
|---|---|
| Early virological response | ≥2-$\log_{10}$ decrease in the HCV RNA level or as an undetectable HCV RNA level by 12 weeks of therapy |
| Nonresponse | <2-log decline in baseline HCV RNA levels after 12 weeks of therapy |
| Partial response | ≥2-log decline in serum HCV RNA occurs, but the virus is detectable after 24 weeks of treatment |
| Sustained virological response | HCV RNA remains undetectable in the serum 6 months after therapy is discontinued |
| Relapse | Reappearance of HCV RNA following treatment withdrawal |
| Rapid virological response | Undetectable serum HCV RNA level at week 4 of treatment |

treatment (pretreatment predictors) or during treatment (on-treatment predictors) is absolutely vital in determining the optimal therapy and duration of treatment. A number of host, genetic and viral factors are responsible for the variable outcome of patients with HCV infection.

## Pretreatment predictors of response

A wide range of pretreatment factors, both viral-related and patient-related are evaluated to determine to predict successful outcome before initiating IFN therapy. However the use of these does not accurately predict SVR in all patients. Also, deciding not to initiate treatment should not be based on the presence or absence of one pretreatment factor. In fact, patients with significant fibrosis benefit most from treatment, although their chances of achieving SVR are less than patients with other favorable characteristics. Although pretreatment indicators are evaluated, the use of on-treatment response indicators provide a more accurate means to assess the end-of-treatment response. Achieving RVR has recently been shown to be important in treatment duration and predicting outcome as studies show that the positive predictive value using RVR for predicting SVR is 89% [Davis *et al.* 2003]. Similarly, patients who achieve complete EVR also have high SVR rates varying from 68% to 84% [Davis *et al.* 2003]. Patients who are slow to respond may benefit from more prolonged treatment to 72 weeks [Berg *et al.* 2006]. Thus, viral kinetics is more useful to determine the probable outcome of treatment.

## Host factors

### *Race/ethnicity*

Race is one of the well-studied but poorly understood host factors that is associated with variable treatment response [Reddy *et al.* 1999]. Several studies have shown that African-American patients are less likely to respond to treatment and achieve SVR as compared to non-African American patients [McHutchison *et al.* 2000; Shiffman *et al.* 2007; Jeffers *et al.* 2004; Muir *et al.* 2004; Conjeevaram *et al.* 2006]. SVR for African-Americans with peg-IFN and RBV varies from 19% to 28% as compared to 39–52% with non-African-Americans [Shifmann *et al.* 2007; Conjeevaram *et al.* 2006; Jeffers *et al.* 2004; Muir *et al.* 2004; McHutchison *et al.* 2000]. Breakthrough viremia is also more common in African-Americans (13% *versus* 6%) [Conjeevaram *et al.* 2006]. The mechanism for the poor response to antiviral treatment is not clear, although is hypothesized to be due to higher body weight and a higher prevalence of genotype 1 infection in African-Americans [McHutchison *et al.* 2000]. There is no clear data however to support this hypothesis. In studies comparing the treatment response in African-Americans as compared with Caucasians with peg-IFN and RBV, poor response rate was seen in all the genotypes of HCV infection [Shifmann *et al.* 2007; Conjeevaram *et al.* 2006; Muir *et al.* 2004; McHutchison *et al.* 2000]. Layden-Almer *et al.* [2003] compared African-American with Caucasian patients and found that African-Americans infected with genotype 1 exhibited significantly lower decreases in first-phase viral RNA, slower elimination of infected cells and smaller declines in mean viral RNA over 1 month suggesting an impaired ability to block viral production in African-Americans [Layden-Almer *et al.* 2003]. Also, Hispanics respond poorly to treatment as compared with Caucasians [Rodriguez-Torres *et al.* 2009; Cheung *et al.* 2005; Hepburn *et al.* 2004]. In a nonrandomized, prospective study of Latino population infected with HCV genotype 1, the rate of SVR was lower in Latinos as compared with non-Latinos (34% *versus* 49%). HCV infection in Latinos is

characterized by more aggressive inflammatory activity and fibrosis and increased progression [Rodriguez-Torres *et al.* 2009]. Latinos had a higher prevalence of insulin resistance and diabetes mellitus and also had more than 33% fatty cells on liver biopsy responsible for decreased rate of SVR [Rodriguez-Torres *et al.* 2006; Harris *et al.* 1998]. Latinos also have a high prevalence of other risk factors associated with a reduced SVR including cirrhosis, HIV co-infection, heavy alcohol consumption and drug abuse [Rodriguez-Torres, 2008; Rodriguez-Torres *et al.* 2006]. People of Asian descent respond favorably when compared with Caucasians achieving a SVR of 65% as compared to 45% in the Caucasian arm [Missiha *et al.* 2007; Hepburn *et al.* 2004].

Variation in the immunogenetic background of HCV-infected individuals might account for some observed racial variations in viral-specific immunity. In a study to explore whether MHC gene variants were associated with response to therapy and racial differences in treatment response, there were potential, but not statistically significant, differences in MHC associations [Rhodes *et al.* 2008]. However, further studies to explore immunogenetics are warranted to understand the racial differences in treatment.

### *Age*

Prospective studies thus far highlight the fact that younger age (age <40) is associated with more SVR [Shiffman *et al.* 2007; Fried *et al.* 2002; Manns *et al.* 2001]. The efficacy and safety of antiviral therapy in the older population is not clear and are limited to small, single-center studies [Koyama *et al.* 2006; Terranova and Luca, 1996]. Immunological suppression, chronic disease and other medication use in the elderly age group can significantly impair the drug response. In a recent report of pooled data from previous studies [Hadziyannis *et al.* 2004; Fried *et al.* 2002], SVR was compared in patients below and above 50 years with genotype 1 infection; there was a significant difference in SVR and EVR [Reddy *et al.* 2008]. However, in patients above 50 years with positive prognostic factors including patients with low HCV RNA levels and those without advanced fibrosis, the SVR rates are comparable with younger patients below 50 years highlighting the importance of other factors in addition to age.

### *Sex*

Previous studies reported that female sex was associated with significant differences in achieving SVR with standard IFN and RBV [Poynard *et al.* 2007]. However, with large prospective studies with peg-IFN and RBV, there is no influence of sex in achieving SVR [Fried *et al.* 2002; Manns *et al.* 2001].

### *Obesity*

Obesity is a predictor of disease progression with hepatitis C infection and prospective studies report that BMI $\geq 25\,kg/m^2$ was associated with significant progression in the extent of fibrosis [Ortiz *et al.* 2002]. Close to 30% of patients with HCV are obese and significantly impairs treatment response [Bressler *et al.* 2003]. Obesity is associated with a reduced response to combination therapy as well as increased steatosis and fibrosis [Hickman *et al.* 2003]. High serum leptin predicts antiviral treatment resistance in patients with low viremia [Eguchi *et al.* 2006]. Leptin is shown to be independently associated with more severe liver fibrosis in chronic HCV patients with a higher BMI [Piche *et al.* 2004]. Although no causal relationship between leptin and steatosis is demonstrated, overweight patients with HCV infection have more steatosis and serum leptin levels [Hickman *et al.* 2003]. Leptin is demonstrated *in vitro* studies to have proinflammatory properties upregulating proinflammatory Th1 cytokines and decreasing the production of the anti-inflammatory cytokines [Mattioli *et al.* 2005; Steinman *et al.* 2003]. The evidence at present to measure leptin to predict treatment outcome is unclear and we do not recommend measuring it routinely. The postulated reasons for the poor response seen in obese patients is due to the presence of hepatic steatosis in obese patients, impaired IFN absorption and altered metabolism due to the production of cytokines from adipocytes [Charlton *et al.* 2006, Jianwu *et al.* 2006]. Although a recent large study did not show any effect of BMI on treatment response [Jacobson *et al.* 2007], weight loss forms an important part of HCV treatment as it lowers liver enzymes and slows the progression of fibrosis independently [Walsh *et al.* 2006; Hickman *et al.* 2002]. Overall, the growing number of patients with pervasive steatosis associated with various comorbidities, continue to plague the potential for success in the HCV patient receiving antiviral therapy.

### *Insulin resistance*

HCV infection is associated with insulin resistance as demonstrated in multiple studies [Zein *et al.* 2005; Thuluvath and John, 2003; Mehta *et al.* 2000]. Also chronic HCV infection is shown to increase the risk of developing diabetes mellitus by up to 11 times in epidemiological studies [Harrison, 2006; Ratziu *et al.* 2004]. Insulin resistance in chronic HCV infection is important in determining treatment outcome as significant correlation is demonstrated between insulin resistance and extent of liver fibrosis [McCaughan and George, 2004]. Studies demonstrate that insulin resistance in animal models is related to high levels of tumor necrosis factor (TNF) [Shintani *et al.* 2004; Larrea *et al.* 1996]. Also, high levels of TNF are seen in patients with chronic HCV infection and have been shown to be associated with decrease response to IFN [Romero-Gomez *et al.* 2005]. In a multivariate analysis of the Virahep-C study, the HOMA index, a measure of insulin resistance, was independently associated with SVR [Conjeevaram *et al.* 2007]. Similar observations were reported in a previous study of genotype 1-infected patients treated with IFN, in which patients with a normal HOMA (<2) had a SVR of 60.5%, compared with 40% in patients with moderate insulin resistance (HOMA 2–4) and only 20% in patients with severe insulin resistance (HOMA > 4) [Romero-Gomez *et al.* 2005]. Insulin resistance may affect treatment response by upregulating SOC3 which blocks IFN mediated signaling [Walsh *et al.* 2006].

### *Alcohol*

Alcohol use is associated with decreased response to standard IFN [Singal and Anand, 2007]. However in a large prospective study, patients who consumed alcohol (≥6 drinks/day) were more likely to discontinue therapy; patients who completed treatment had a comparable response as patients who did not drink [Anand *et al.* 2006]. However, prospective studies highlight that both histological activity and fibrosis increase with the amount of alcohol use and that even moderate alcohol consumption, as low as 31–50 g/day in men and 21–50 g/day in women, accelerates the histological lesions in chronic HCV patients [Hezode *et al.* 2003; Poynard *et al.* 1997]. HCV patients who drank more than 50 g/day had a 34% increased rate of fibrosis as compared with those who drank less [Poynard *et al.* 1997].

### *Genetic diversity*

Several studies investigated the role of host genetic factors modulating the response to antiviral treatment and viral clearance. Nonresponders have elevated gene expression of interferon-stimulated genes (ISGs) in their IFN regulation pathway and this may have a predictive value in HCV treatment [Sarasin-Filipowicz *et al.* 2008; Feld *et al.* 2007; Chen *et al.* 2005].

ISGs are elevated at baseline in nonresponder liver tissue when compared with responders; however, these elevated ISGs do not clear or control HCV infection [Sarasin-Filipowicz *et al.* 2008; Feld *et al.* 2007; Chen *et al.* 2005]. Also, nonresponders do not have ISG induction over baseline with treatment because baseline ISG expression is elevated already [Huang *et al.* 2007]. The absence of induction in nonresponders is mediated probably by inhibitory proteins such as SOCS3 which blocks IFN signaling [Tai and Chung, 2009].

A recent study reported the expression of three genes (IFI-6-16, IFI27 and ISG15) coding for IFN-inducible proteins was upregulated in nonresponders to antiviral therapy and the presence of two-gene signature including one of the three genes (IFI27) predicted treatment outcome fairly well [Asselah *et al.* 2008]. Studies also highlight that protein kinase (PKR) mRNA levels in peripheral blood mononuclear cells (PBMC) and the liver correlated with nonresponse [Taylor *et al.* 2007]. Recently, single nucleotide polymorphisms (SNPs) of suppressor of cytokine signalling 3 (SOCS3) was associated with variable response to antiviral therapy in hepatitis C virus (HCV) genotype-1-infected patients [Persico *et al.* 2008].

HFE gene polymorphisms (both the C282Y and the H63D mutation) also influence response to IFN therapy as has been demonstrated in recent studies [Bonkovsky *et al.* 2006; Lebray *et al.* 2004]. The underlying mechanisms, however, have not been clearly delineated. The presence of HFE mutations is associated with high hepatic iron concentration, which is inversely associated with treatment response in other studies (see below) [Bonkovsky *et al.* 2006]. Although genetic polymorphisms are implicated in the variable treatment response seen in patients, none of them have been validated in routine clinical use. We do not routinely test for HFE gene polymorphisms before initiating treatment as the

evidence for guiding treatment based on these are not clear.

Hepatic iron concentration (HIC) also is proposed as a cause of varying response. The pathogenesis of HIC however is unclear, although heterozygosity for hereditary hemochromatosis (i.e. C282Y heterozygosity) is proposed for iron overload [Gehrke *et al.* 2003]. Although initial studies demonstrated that hepatic iron accumulation impairs response to standard IFN therapy, especially in genotype-1 infected individuals [Barbaro *et al.* 1999; Fargion *et al.* 1997; Olynyk *et al.* 1995] in recent trials HIC did not predict response to combination therapy [Hofer *et al.* 2004; Fracanzani *et al.* 2001].

### *Histological parameters*

Liver biopsy is the gold standard to assess HCV severity. It also helps to establish the histologic grade and disease stage, which provide prognostic information and to assess patient's response to antiviral therapy. However, there is high interobserver variability in histopathologic interpretation and varying scoring systems. We usually perform liver biopsy when initiating treatment. However, we do not serially repeat biopsies and follow patients with noninvasive tests.

With regard to the grading of liver biopsy findings, different scores are used. The Knodell histological activity index (HAI) is based on following changes, piecemeal, periportal, bridging and multilobular necrosis; intralobular degeneration and focal necrosis; inflammatory cell density in the portal tracts; and the degree of fibrosis and cirrhosis with scores ranging from 0 to 22 [Knodell *et al.* 1981]. However, the combination of fibrotic changes with progressive changes and the clumping of piecemeal and bridging necrosis in the same category does not help in detecting progression [Goodman and Ishak, 1995; Ishak *et al.* 1995]. The Ishak system modifies and separates scoring for necroinflammation and fibrosis [Ishak *et al.* 1995]. The METAVIR system widely used in Europe developed for hepatitis C grades based on portal and lobular necroinflammatory activity, scored from 0 to 3; and fibrosis/cirrhosis, scored from 0 to 4 [Bedossa and Poynard, 1996]. The METAVIR system is particularly advantageous and easy to grade when compared with the other systems.

Studies show that the presence of advanced fibrosis and cirrhosis is a major independent predictor of nonresponse to antiviral therapy [Everson *et al.* 2006; Poynard *et al.* 2000]. In a large study of 1744 naive patients with chronic HCV infection undergoing IFN treatment, the presence of no fibrosis or fibrosis limited to the portal tract alone was independently associated with SVR on multivariate analysis [Poynard *et al.* 2000]. The presence of fibrosis and cirrhosis is also determined by the host immune system. Hepatic steatosis in chronic HCV infection is associated with changes in the immune cells. Helper T cells are skewed towards a predominant Th-1 cytokine response promoting increase in proinflammatory cytokines [Palmer *et al.* 2009; Kremer *et al.* 2006]. Cytokines play a major role in the pathogenesis of liver fibrosis and are secreted in response to initial liver injury by HCV. The balance between the proinflammatory cytokines like transforming growth factor, IL-10 and the anti-inflammatory cytokines determine the extent of fibrosis [Napoli *et al.* 1996]. In addition to these, genetic predisposition, comorbid diseases (i.e. hemochromatosis, HIV coinfection) may worsen the progression of fibrosis [Benhamou *et al.* 1999; Poynard *et al.* 1997]. In fact, in a large study involving 4913 patients with HCV genotypes 1–3 infection, multivariate regression analyses identified the absence of cirrhosis as a predictor of SVR [Jacobson *et al.* 2007].

The frequency of steatosis in chronic HCV infection is around 50%, significantly higher in patients with genotype-3 infections [Rubbia-Brandt *et al.* 2004; Castera *et al.* 2003]. Steatosis is suggested to be independently associated with progression of fibrosis and in a recent meta-analysis of more than 3000 patients with chronic HCV infection from Europe, Australia, and the US, steatosis was significantly and independently associated with fibrosis in these patients [Leandro *et al.* 2006]. Also, the presence of steatosis was associated with impaired response to antiviral treatment and decreased rate of SVR [Leandro *et al.* 2006].

## Virological factors

### *Hepatitis C quasispecies variation*

Hepatitis C virus exists as a quasispecies, defined by the presence of closely related variants that are genetically distinct [Pawlotsky, 2006]. These variants provide HCV with the property to escape host defences and resist clearance by antiviral therapies [Pawlotsky, 2006]. Thus, patients with minimal HCV complexity (i.e. small quasispecies

sequence) achieve SVR than patients with large HCV complexity and variation in the quasispecies composition [Pawlotsky, 2006, 2003]. In addition to the quasispecies variation, mutations within specific regions of the HCV genome (i.e. the NS5A region) also contribute to the varying response [Pascu *et al.* 2004]. However, the use of quasispecies in predicting outcome is not used routinely and remains predominantly a research tool.

### *HCV baseline RNA viral load*

Viral load assessment before, during and after therapy is an important tool for predicting the treatment outcome. Although viral load does not correlate with the severity of liver injury or the progression of the disease, a low baseline viral load (<600,000–800,000 IU/ml or less) is an independent predictor of SVR regardless of genotype in many studies [Zeuzem *et al.* 2006; Berg *et al.* 2003; Manns *et al.* 2001; Poynard *et al.* 1998] and patients with pretreatment high viral loads have worse long-term outcomes than patients with low viral loads and the relationship is nonlinear.

### *HCV genotype*

HCV genotype is one of the important baseline predictor for response to antiviral combination therapy with IFN-alpha and RBV. HCV genotype 1 is associated with lower rates of SVR compared with other genotypes [Shiffman *et al.* 2007; Jacobson *et al.* 2007; Fried *et al.* 2002; Manns *et al.* 2001; Poynard *et al.* 2000]. Genotype 4 and 6 is also associated with decreased responsiveness but may be better than genotype 1 [Shiffman *et al.* 2007; Jacobson *et al.* 2007; Fried *et al.* 2002; Manns *et al.* 2001; Poynard *et al.* 2000].

Genotype-1 infected patients achieve a SVR ranging from 41–52% after 48 weeks of peg-IFN plus RBV as opposed to 76–84% in genotypes 2 and 3 [Shiffman *et al.* 2007; Fried *et al.* 2002; Manns *et al.* 2001]. On a similar note, genotype 4 patients treated for 48 weeks showed response rates at an intermediate level compared to genotype 1 and genotypes 2 or 3, with SVR rates between 65% and 72%, as recently described [Alfaleh *et al.* 2004, Hasan *et al.* 2004; Khuroo *et al.* 2004]. Unfortunately, no large randomized trials of genotypes 5- and 6-infected patients have been conducted to date and the treatment response is unclear.

In a recently published meta-analysis of published studies on genotype 2 and 3 infection, SVR rates were 74% and 68% respectively [Andriulli *et al.* 2008]. In patients with high viral loads (>600,000 IU/ml), SVR rate in genotype-2 infection was 75% in contrast to 58% in genotype-3 infection; with low viral loads (<600,000 IU/ml) was 79% and 75% respectively [Andriulli *et al.* 2008].

The reasons for the varying virologic response in different HCV genotypes are complex and not yet fully understood. Viral kinetic analyses results suggest that hepatocytes infected with genotype 1 have a lesser clearance of the virus and antiviral efficacy is reduced in patients infected with HCV genotype 1 compared with infections with other HCV genotypes [Zeuzem *et al.* 2001; Neumann *et al.* 2000].

## On-treatment predictors of response

### *Viral kinetics*

The behavior of antiviral medications is studied by following viral kinetics to establish algorithms for individualized treatment. Biphasic response to IFN-based treatment occurs and rapid reduction of HCV RNA happens within the first 24–48 h reflecting the blocking of viral production and the subsequent slower log-linear decline represents the clearance of infected hepatocytes [Neumann *et al.* 1998; Zeuzem *et al.* 1996]. Determination of viral kinetic parameters of the second phase; that is, the rate of infected cell loss correlates with sustained virological response [Pilli *et al.* 2007; Herrmann *et al.* 2003; Layden *et al.* 2002a, 2002b; Lam *et al.* 1997].

### *Assessment of response to antiviral therapy after 4 weeks of treatment*

Assessment of serum HCV RNA at week 4 of therapy is increasingly recognized as one of the most important determinants of treatment response. Rapid viral response (RVR) defined by absence of HCV RNA at week 4 of therapy is an independent predictor of SVR. In a large retrospective study involving 1383 patients of all genotypes, results show that RVR accurately predicts SVR as patients who achieve RVR have an 86–100% probability of SVR to peg-IFN/RBV combination therapy, irrespective of genotype [Fried *et al.* 2008]. Thus, even in genotype-1 infected patients, who require 48 weeks treatment traditionally, shortening the duration of treatment to 24 weeks instead of 48 weeks is

possible if low (<600,000–800,000 IU/ml) baseline viral load and a RVR is present. SVR rates of >75% are reported in a number of studies involving both peg-IFN alpha and RBV [Ferenci *et al.* 2008; Jensen *et al.* 2006]. Thus, the initial response to treatment is being considered a more important predictor of treatment duration and SVR rather than the genotypes as was initially thought to determine the probable outcome of treatment. The positive predictive value using RVR for predicting SVR is 89%; however, the negative predictive value is only 61%. Thus, the criterion of nondetectable HCV RNA by PCR at 4 weeks of treatment should not be used for early discontinuation of therapy [Davis *et al.* 2003].

In patients with genotype 2/3 infection, studies show that shortening the duration of treatment to 12–16 weeks instead of the traditional 24 weeks in patients who achieve an RVR is feasible [Dalgard *et al.* 2008, 2004; Mangia *et al.* 2005]. However, in a recently published larger trial suggested that treatment shortening to 16 weeks should be considered only for patients with an RVR and low baseline viral load (<800,000 IU/ml) only and treatment to 24 weeks should be done in other patients [Shiffman *et al.* 2007]. However, most of these studies published thus far are from Europe and may not be completely applicable to patients in the US, who have a higher BMI and may have a higher level of insulin resistance. Also, in a recently published article reviewing evidence for shortening therapy in HCV, the authors concluded that there is a lack of evidence that all HCV patients who achieve RVR would benefit from shorter treatment durations as patients with high viral loads had a higher relapse rate with shortening treatment [Nelson *et al.* 2009].

### *Assessment of response to antiviral therapy after 12 weeks of treatment*

Until recently, assessment of serum HCV RNA at week 12 of therapy was recognized as one of the most important determinants of treatment response. Early virologic response (EVR) is defined by viral load decline greater than 2 $\log_{10}$ or undetectable HCV RNA at week 12.

Earlier studies highlighted that the SVR rate at 72 weeks was 67% with chronic HCV infection who achieved early virological response with peg-IFN alpha and RBV at week 12 (HCV RNA negative or 2 $\log_{10}$ decrease) in contrast to SVR rate of only 3% among those who did not show a 2-$\log_{10}$ decline or achieve undetectable HCV RNA at week 12 [Ferenci *et al.* 2005; Davis *et al.* 2003; Fried *et al.* 2002]. This led to the implementation of a stopping rule for patients without EVR irrespective of genotype at week 12.

However, subsequent studies show that patients with genotype 1 have a differential viral kinetics response to treatment and a subset of patients with genotype 1 are slow to respond, but respond eventually. Thus, rates of SVR in genotype-1 infected patients achieving an EVR are heterogeneous. Thus, patients infected with genotype-1 with a complete EVR can achieve high SVR rates (68–84%) with peg-IFN alpha and RBV combination therapy, if the treatment is prolonged for 48 weeks, unlike patients with a partial EVR (2 $\log_{10}$ decline but still HCV RNA positive at week 12) who achieved an SVR of only 17–29% if treated for 48 weeks [Berg *et al.* 2006]. This particular subset of slow to respond patients may benefit from treatment prolongation to 72 weeks as also supported by other subsequent trials which were able to achieve a better SVR [Mangia *et al.* 2008; Pearlman *et al.* 2007; Sanchez-Tapias *et al.* 2006].

Thus, subdividing patients with genotype 1 into patients who achieve EVR into complete EVR (HCV RNA < 50 IU/ml at week 12) or partial EVR (>2 $\log_{10}$ drop in HCV RNA but still detectable [>50 IU/ml]), we can tailor treatment duration in individual patients. The data in patients with genotype 2/3 who achieve partial EVR is unclear as there are no long-term studies. However, 90% of patients with HCV genotype 2/3 infection achieve a complete EVR and thus in this group of patients, tailoring treatment duration is based on whether they had achieved RVR at 4 weeks treatment. Patients who do not achieve RVR, but achieve EVR at 12 weeks treatment should be considered for 48 weeks treatment.

### *Assessment of response to antiviral therapy after 24 weeks of treatment*

Patients who achieve partial EVR (>2 $\log_{10}$ drop in HCV RNA but still detectable [>50 IU/ml]) who continue treatment for 24 weeks and still are HCV RNA positive fail to achieve SVR in 98–100% of instances. There is no role for continuing treatment in this subset of patients [Berg *et al.* 2006; Sanchez-Tapias *et al.* 2006]. However, patients who are slow to respond, the slow responders (partial EVR at 12 weeks,

but HCV RNA negative at 24 weeks); this particular subset of patients may benefit from treatment prolongation to 72 weeks as also supported by trials which were able to achieve a better SVR [Mangia *et al.* 2008; Pearlman *et al.* 2007; Sanchez-Tapias *et al.* 2006]. SVR rates were significantly higher among those treated for 72 weeks than among those treated for 48 weeks (45% *versus* 32%; $p = 0.014$) [Sanchez-Tapias *et al.* 2006].

Slow responders account for 22% of HCV-infected patients and extending therapy to 72 weeks is shown thus far to improve SVR [Mangia *et al.* 2008]. Thus, the current evidence supporting prolonging duration of treatment to 72 weeks is growing in patients who are slow to respond [Nelson *et al.* 2009]. The various studies are summarized in Table 2.

### *Treatment algorithms for early discontinuation of nonresponders*

Thus far we had focused on the development of treatment algorithms for determination of the duration of treatment based on response at weeks 4, 12 and 24. However, to make a decision to discontinue treatment is a big decision and for designing the algorithm for discontinuation of therapy in patients without a chance for achieving a SVR, the negative predictive value (NPV, proportion of patients without SVR in the group of all patients without early virologic response (EVR)) is of special importance. The NPV should ideally be 100% to avoid premature withdrawal of therapy in patients who might still have a chance for achieving sustained virologic response. Although there are no definite studies or guidelines to decide when to stop treatment, we would definitely stop treatment at 24 weeks when the patients are still HCV RNA positive as the possibility of achieving SVR is less than 1% if the treatment is continued beyond that point. However, the rationale is to stop treatment earlier than that rather than needlessly exposing patients to 24 weeks treatment who are definitely not going to respond. Unfortunately, there are no treatment guidelines to make the decision. In our observations, patients with HCV RNA levels that do not decline beyond 20–30% from baseline after 8 weeks of treatment are unlikely to respond to treatment in the long run. However, we require prospective large studies to decide when to stop these medications and decide about pursuing newer treatments and enrolling patients in clinical trials involving experimental therapy.

## Adherence to treatment

Adherence is defined as the extent to which the patient continues the agreed upon mode of treatment under limited treatment supervision. Poor adherence to treatment is an issue in diseases requiring long-term treatment, which results in poor health outcomes and increased health care costs – hepatitis C is no exception to this [Simpson *et al.* 2006; Osterberg and Blaschke 2005].

Adherence plays a major role in SVR, as shown by McHutchison *et al.* [2002] who demonstrated that SVR significantly improved in patients with HCV genotype-1 infection who received >80% of their total peg-IFN dose and >80% of their RBV dose for >80% of the scheduled treatment duration, in comparison with those who failed these adherence criteria [McHutchison *et al.* 2002]. Adherence influences treatment response independently of HCV genotype and viral load [Hughes and Shafran, 2006]. The major predictors of poor adherence include treatment of asymptomatic disease, presence of coexisting depression, patient's lack of belief in treatment, complexity and side effects of treatment [Osterberg and Blaschke, 2005].

**Table 2.** Extension of duration of therapy to 72 weeks in slow-to-respond patients.

| Study | Duration | SVR | Relapse | Comments |
|---|---|---|---|---|
| Sanchez-Tapias *et al.* [2006] | 48 | 28 | 53 | SVR increased in patients who did not achieve RVR |
| | 72 | 44 | 17 | |
| Berg *et al.* [2006] | 48 | 17 | 64 | SVR improved in slow to respond patients alone |
| | 72 | 29 | 40 | |
| Pearlman *et al.* [2007] | 48 | 18 | 59 | SVR improved in slow to respond patients. |
| | 72 | 38 | 20 | |
| Ferenci *et al.* [2006] | 48 | 31 | 63 | SVR improved in slow to respond patients |
| | 72 | 77 | 23 | |

RVR, rapid virologic response; SVR, sustained virologic response.

Patient education significantly improves adherence to treatment as has been shown with RBV, which in turn improves to SVR as shown in chronic disease [Mulhall and Younossi, 2005]. Education required the cooperation of specialists and nursing staff, and therefore probably affected both patient-related and healthcare team-related factors, which are recognized to improve adherence [Osterberg and Blaschke, 2005].

## Future directions

Pre- and on-treatment predictors are important tools for successful treatment in chronic HCV infection. We have come a long way since the introduction of IFN monotherapy to achieve a SVR up to 63% with combination peg-IFN and RBV. The kinetics of viral response may help us to tailor therapy individually in patients with HCV infection allowing us to prolong therapy up to 72 weeks in patients who are likely to respond and stopping patients as early as possible if the response is less likely to occur. However, the present problem we face is to decide when to stop the treatment in situations in which patients are unlikely to respond.

RVR is rapidly becoming a new tool for predicting patients with hepatitis C who are more likely to achieve SVR. In addition, it may identify patients for whom a shortened course of therapy is appropriate. RVR is an important point at which strategies for treatment regimens can be evaluated. In the future, even early prediction of response may be feasible. In a small study by Magalini *et al.* [2000] the lack of response after just 3 days of treatment with IFN with failure to achieve an 85% reduction in HCV RNA negatively correlated with RVR and correlated with SVR [Magalini *et al.* 2000]. RVR is a new tool and would be potentially cost effective if predictability parameters are based at that time. Also, the NPV at week 8 is 95%, and makes week 8 an important decision point. Strategies based on evidence-based trials are required as the patients who are unlikely to respond to IFN-based treatment may be provided with an alternative treatment plan. Also, the sequencing of the human genome will offer unique opportunities and genome-wide association studies will help us better target antiviral therapy to individual patients, particularly in patients with difficult-to-treat patient groups. For example, basal levels of SOCS3, an inhibitor of the IFN alpha-induced Janus kinase-signal transducer and its genetic polymorphisms influence the outcome of antiviral treatment [Su *et al.* 2008]. Su *et al.* also reported that in a cohort of genotype-1 patients, single nucleotide polymorphisms in interferon signaling pathway genes and IFN-stimulated genes was associated with SVR [Persico *et al.* 2007]. Other genes that are being studied include transforming growth factor beta, microsomal epoxide hydrolase gene, apolipoprotein E-epsilon 4, keratin variants, hyperhomocysteinemia and the MTHFR C677T polymorphism, DDX5 minor allele or DDX5-POLG2 haplotypes, SLC11A1 promoter gene, and the MCP-1 gene [Huang *et al.* 2006; Strnad *et al.* 2006; Adinolfi *et al.* 2005; Romero-Gomez *et al.* 2004; Muhlbauer *et al.* 2003; Sonzogni *et al.* 2002; Wozniak *et al.* 2002; Powell *et al.* 2000].

Also, multiple studies show that insulin resistance is independently associated with SVR and development of therapies to reverse insulin resistance and study its effect on SVR is underway. However, whether reversal of insulin resistance results in higher rates of HCV treatment response *in vivo* and translates to an increase in SVR is unclear. Clinical trials are underway to determine whether addition of insulin sensitizers, such as thiazolidinediones, to current HCV therapy will increase SVR [Tai and Chung, 2009].

Development of proteomics for determining response to HCV infection is being studied. Protein signatures might provide a potentially powerful tool in diagnostics and prognostics. Jacobs *et al.* [2005] studied the proteome changes in HCV infection and reported the upregulation of several proteins involved in lipid biosynthesis and downregulation of proteins involved in fatty acid oxidation. Although all these techniques are in infancy in predicting the response to treatment in HCV infection, these may provide opportunities in the future to individualize treatment.

Thus, the recent development of genomic and proteomic technologies provide potential opportunities to expand our tools in predicting disease outcome including response to therapy in patients with HCV infection. The development of a composite mathematical model incorporating all the determinants of treatment response will be useful to predict the treatment outcomes of patients with HCV infection.

## Conclusion

A number of host, genetic and viral factors interact to predict the probable outcome of patients with HCV infection. HCV genotype other than 1 and low baseline viral load are the most important baseline predictors of SVR. RVR has become an important determinant of treatment duration irrespective of the genotype and the presence or absence of other determinants and has come to be recognized as one of the most powerful predictors of SVR. However, our understanding of the variable response in different patients is still unclear and more research is required to further elucidate the complex interactions between the virus and the host response.

## Conflict of interest statement

None declared.

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