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Predicting the therapeutic response in patients with chronic hepatitis C: the role of viral kinetic studies

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A substantial proportion of patients infected with hepatitis C virus (HCV) genotype 1 still does not respond to pegylated interferon-alfa/ribavirin (IFN/RBV) therapy. Factors which identify potential non-responders are needed to limit exposure to drugs in patients unlikely to benefit from treatment and to save health care resources. Host predictive factors have a low negative predictive value. In contrast, viral factors have a high precision in predicting outcome of therapy. Viral kinetics are the basis for the study of response of therapy. The decrease in viral load within 24 h after administration of a single test dose of conventional IFN reflects the IFN-sensitivity of the virus strain and predicts the outcome of conventional IFN/RBV therapy even before treatment with a specificity of 100% and a sensitivity of 83%. In contrast to conventional IFN, the two available PEG-IFN preparations differ considerably in how they suppress viral replication, and cut-off values have to be prospectively established separately for each drug. Patients without an early virological response (HCV-RNA either undetectable or decrease by ≥2 $\log_{10}$ after 12 weeks) (EVR), do not achieve a sustained virological response (SVR; negative predictive value: 97–98%). Thus, in the absence of an EVR, treatment should be stopped. The outcome of PEG-IFN alfa-2a/RBV combination therapy is dependent on the rapidity of the virological response. Patients who become HCV-RNA negative after 4 weeks have the best chance of achieving an SVR. The rapidity of viral elimination may be a useful guide to tailoring the length of treatment in patients with an EVR.

Keywords: HCV, therapy, outcome prediction

Introduction

In the 15 years since characterization of the hepatitis C virus (HCV),[1] understanding of the natural history of chronic hepatitis C has greatly expanded, and more effective therapeutic strategies have been developed. Sustained virological response (SVR) rates have been improved from >20% of patients treated for 48 weeks with conventional interferon (IFN) alfa, to ≈40% of patients treated with the combination of IFN alfa-2b plus ribavirin,[2,3] and 54–61% of patients treated with a pegylated IFN and ribavirin,[4–6] the current treatment of choice.[7] As a substantial proportion of patients do not respond to treatment, especially those infected with HCV genotype 1, much work remains to be done to optimize treatment for chronic hepatitis C.

Background

The study of HCV dynamics is rooted in models developed to describe HIV infection,[8] and has been facilitated by the development of sensitive and specific quantitative assays for HCV-RNA. Changes in viral load over time reflect changes in the production and/or elimination of the virus and allow the assessment of the ability of the infected host to clear the virus spontaneously and to respond to antiviral therapy.

The first line of host defence is the activation of multiple signalling cascades to produce cytokines that stimulate immune responses. To establish a chronic infection, the virus must bypass host defence mechanisms. IFNs are the most important components of the innate host defence. The interaction between HCV envelope protein E2 and double-stranded RNA-activated protein kinase (PKR) may be one mechanism by which HCV circumvents the antiviral effect of IFN.[9–12] IFN regulatory factors (IRF) -3 and -7 are major regulators of IFN production.[13] IRF-3 is directly activated after virus infection and stimulates the expression of alpha/beta IFN early in infection;[14] IRF-7 amplifies the expression of other IFN genes in later stages of infection.[15] A serine protease associated with the NS3/4 protein of HCV inhibits IRF-3 activation,[16] and thereby IFN production. The interference of HCV with IFN activation and signalling results in IFN-resistant virus strains which are unlikely to respond to IFN-based therapies.

The early host defence can be investigated in patients acutely infected with HCV. Recently, 12 patients with acute hepatitis C were investigated.[17] Although there was no difference in HCV-RNA titres at the onset of symptoms, HCV-RNA levels declined rapidly and

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continuously in patients who experienced spontaneous viral clearance but remained constant or increased after the onset of symptoms in those who did not clear the virus.[17] In contrast to patients developing chronic hepatitis C, patients clearing the virus spontaneously have a vigorous cellular immune response to HCV.[18,19] The mean time from exposure to the virus, and from the onset of symptoms, to HCV-RNA negativity was 77 and 35 days, respectively. Thus, repeated quantification of HCV-RNA levels identified patients not needing antiviral therapy.

Viral kinetics as a tool to predict response to antiviral therapy in chronic hepatitis C

HCV-RNA levels in untreated patients with chronic hepatitis C do not vary over time[20] and do not correlate with alanine aminotransferase (ALT) levels and liver histology,[21] suggesting that a dynamic equilibrium exists in which virion production is balanced by viral elimination.[20] IFN-based therapies reduce HCV levels by blocking viral replication, inhibiting release of virions and inducing immune clearance of infected cells.

Viral kinetics on treatment with conventional IFN

The initial biphasic decline in HCV-RNA can only be studied if IFN is continuously present (i.e. on daily IFN). The first decline in HCV-RNA levels is steep and becomes apparent within 24 h after the initiation of treatment and is the result of a blockade of virion production and release. The slope is dose-related over a range of 3–10 million units (MU) of conventional IFN alfa.[22,23] Since it reflects the sensitivity of the virus strain to conventional IFN, it may predict the outcome of therapy even before treatment. A decrease of <70% in HCV-RNA levels within 24 h of a single 5 MU test dose of conventional IFN alfa correlated with non-response to a 48 week course of IFN alfa and ribavirin in patients infected with HCV genotype 1 or 4, with a specificity of 100% and a sensitivity of 83%.[22,24–26] The test is rarely used in the clinical setting. The greatest impact of IFN sensitivity testing is in clinical studies where it allows one to stratify patients to obtain homogenous study groups. It may also be of value if the indication for initiation of antiviral combination therapy is debatable.

The second elimination phase is slower and reflects immune-mediated clearance of HCV-infected cells. The slope of this phase is correlated with the probability of achieving a sustained virological response (SVR).[27]

Ribavirin increases SVR rates by an as yet unidentified mechanism. Ribavirin does not enhance the first or second viral elimination phases; however, a third elimination phase became apparent in some patients treated with peginterferon alfa-2a and ribavirin, but not in those treated with peginterferon alfa-2a alone.[28] The slope of this phase was correlated with SVR rates, a phenomenon interpreted to represent enhanced degradation of infected cells.[28]

IFN sensitivity varies with HCV genotypes. The slope of the first phase decline is steeper in patients infected with HCV genotypes 2 or 3 than genotype 1.[27,29] This correlates with the difference in SVR rates between these subgroups. Also the second phase response is steeper in patients harbouring HCV genotypes 2 or 3.[27] The latter finding may explain why viral eradication may be accomplished in 24 weeks in these patients, whereas a full 48 week course of treatment is needed in patients infected with HCV genotype 1.[5]

Viral kinetic studies may explain why lower SVR rates are found in patients of African-American heritage compared with the overall population.[30]

Viral kinetics on treatment with pegylated IFNs

When conventional IFN alfa is administered on a thrice-weekly schedule, HCV-RNA levels fluctuate in concert with serum concentrations of the drug.[27,31] Administering the drug on a daily basis dampens the fluctuations and provides more sustained suppression of HCV-RNA levels. Pegylated IFNs were developed, in part, to improve the pharmacokinetic properties of IFN and to allow for extended dosing intervals. The difference in pharmacokinetic properties between the two commercially available pegylated IFNs [Peginterferon alfa-2a (PEGASYS, Roche) and pegylated IFN alfa-2b (Pegintron, Schering Plough)] is reflected in distinct viral kinetics.

The extent of viral suppression mirrors serum levels of pegylated IFN alfa-2b. This drug has a terminal elimination half-life ($t_{1/2}$) of ≈40 h in patients with chronic hepatitis C, and serum concentrations generally fall below the limit of detection before the end of the 1 week dosing interval.[32] Viral kinetic studies have revealed an association between the decrease in serum drug concentrations and a rebound in serum HCV-RNA levels.[33,34] The decrease in HCV-RNA levels was dose-related in patients infected with HCV genotype 1; patients treated with 3 μg/kg of pegylated IFN alfa-2b had lower HCV-RNA levels at 24 and 48 h than those who received a 0.5 μg/kg dose ($P < 0.001$). Nonetheless, a significant rebound in HCV-RNA levels was observed in both groups.[33] The rebound in HCV-RNA levels occurred between 48 and 72 h after once weekly administration of pegylated IFN alfa-2b. A similar rebound in HCV-RNA levels was observed in patients infected with HCV genotype 1 who were treated with pegylated IFN alfa-2b, 1.0 μg/kg per week, but was abrogated by twice-weekly administration of the same dose.[34] Formann *et al*.[34] measured serum levels of the drug and, similar to the results of a previous pharmacokinetic study,[32] serum concentrations of pegylated IFN alfa-2b fell to below the limit of detection when the drug was administered once weekly, but remained relatively stable when given twice weekly. Taken together these results demonstrate that, when administered once weekly, serum concentrations of pegylated IFN alfa-2b decrease to the point at which HCV-RNA replication resumes and viral rebound occurs. The optimal regimen of the drug would presumably involve twice weekly administration of a higher dose, at least during a short induction phase.[33,34]

Peginterferon alfa-2a has a $t_{1/2}$ of ≈80 h and plasma levels of the drug are sustained with little peak-to-trough fluctuation. Thus, when given at the approved dose, 180 μg once weekly, suppression of HCV-RNA replication is generally maintained throughout the 1 week dosing interval. The viral kinetics and predictive value of IFN sensitivity testing differ between peginterferon alfa-2a and conventional IFN alfa. In patients infected with HCV genotype 1, the viral decline during the first 2 weeks of treatment with peginterferon alfa-2a 180 μg once weekly was somewhat lower than that reported for conventional IFN alfa.[35] However, the viral rebound typical of alternate day administration of conventional IFN alfa or weekly administration of pegylated IFN alfa-2b was observed only in a minority of patients during treatment with peginterferon alfa-2a.[35] The log change in HCV-RNA levels 24 h after the first dose of peginterferon alfa-2a was similar in those identified as responders and non-responders (log change in HCV-RNA >0.8 and <0.8, respectively) by sensitivity testing with conventional IFN alfa. Moreover, 50% of those identified as likely non-responders by IFN sensitivity testing had a virological response after 24 weeks of treatment with the combination of peginterferon alfa-2a and ribavirin.[35] Thus,

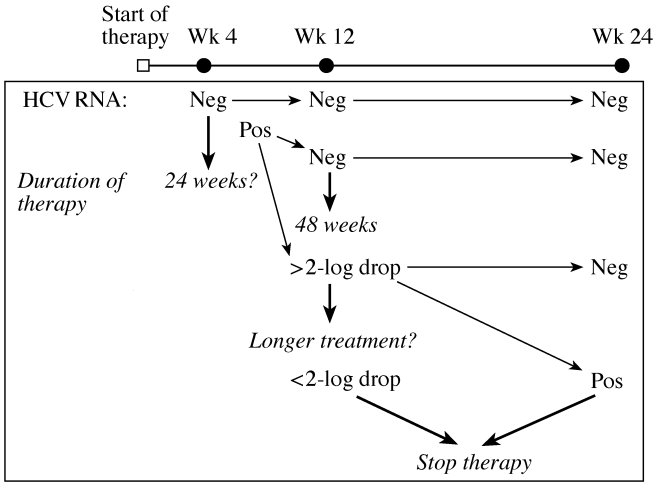

Figure 1. Proposed model for predicting the duration of combination therapy with peginterferon alfa-2a and ribavirin.

peginterferon alfa-2a may overcome predicted unresponsiveness to conventional IFN.

Clinical application of viral kinetics in the treatment of patients with chronic hepatitis C

Viral kinetics has a practical application in the management of patients with chronic hepatitis C (Figure 1). Very few patients without an early virological response (EVR), defined as undetectable HCV-RNA or ≥2 $\log_{10}$ decrease in HCV-RNA levels after 12 weeks of combination therapy, achieve an SVR (negative predictive value: 97–98%). For this reason, HCV-RNA levels should be routinely measured after 12 weeks and, in the absence of an EVR, treatment should be stopped.[7] This strategy limits exposure to drugs in patients unlikely to benefit from treatment and saves health care resources. As with conventional IFN/ribavirin combination therapy,[36] the outcome of combination therapy with peginterferon alfa-2a and ribavirin is highly dependent on the rapidity of the virological response. Patients who become HCV-RNA negative after 4 weeks have the best chance of achieving a sustained virological response. It may be hypothesized that to decrease the frequency of relapse in the remaining patients, treatment longer than 48 weeks may be required.[37]

Impact of adherence on treatment response

Patient adherence with combination therapy exerts a significant influence on SVR rates. Missed doses result in a relaxation of antiviral pressure and resumption of viral replication. In a retrospective analysis, patients with adherence rates of ≥80% had higher SVR rates than those who were less adherent (i.e. those who consumed <80% of prescribed doses).[38] Not surprisingly, the influence of adherence on SVR rates was most marked in patients infected with the more treatment-resistant HCV genotype 1 than in those infected with HCV genotypes 2 or 3. A failure to completely suppress HCV-RNA levels, or an increase in HCV-RNA levels detected by a sensitive and specific assay, may indicate poor adherence to a prescribed regimen, and illustrates the importance of monitoring HCV-RNA levels during treatment.

In summary, viral kinetic studies have provided an explanation for the differential responses according to HCV genotype and allow us to identify patients unlikely to respond to treatment early during therapy. Further research will refine our ability to individualize the dose and duration of therapy for particular patients, especially those infected with HCV genotype 1.

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