Predicting antiviral treatment response in chronic hepatitis C: how accurate and how soon?

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Introduction

The King of Babylon stood at the parting of the ways, to use divination:

He made his arrows bright, he consulted with images, he looked in the liver.

Ezekiel 21: 21

Twenty-six centuries later, things have changed: ancient people wanted to predict future possibilities by means of the liver, whereas now we want to predict the future of the liver by any possible means. Today, hepatitis C virus (HCV), which probably did not exist at the time of the Babylonian Empire,[1] chronically infects 170 million people worldwide, and can lead to liver failure and hepatocellular carcinoma.[2,3] A mere decade ago, the best antiviral therapies produced a long-term virological remission (sustained virological response, SVR) in only 5–10% of treated patients, but significant advances in treatment have increased the SVR rate almost 10-fold to 54–61%. These high response rates were obtained by modifying the standard interferon α by attaching a polyethylene glycol (PEG) moiety (pegylation) to produce a longer-active peginterferon.

SVR, defined as undetectability of HCV RNA 6 months after stopping treatment, is a highly desirable outcome, as >95% of patients with SVR continue to show undetectable HCV RNA indefinitely, i.e. have permanent viral eradication. Unfortunately the peginterferon + ribavirin regimens have a number of drawbacks. Intolerable side effects necessitate prematurely stopping treatment in ~15% of patients, and dose reductions in another 20–40%. Moreover, the drug regimen is very expensive (~US$26 000 for a 48 week course), which means that most patients in countries such as Egypt, which has 10–12 million infected individuals, cannot afford this therapy.[4,5] For these reasons, cost-effective use of this therapy is essential. Accordingly, the ability to accurately predict the response of patients to antiviral therapy is of great interest. In general, predictors may be clinical, biochemical or histological. They can be assessed before therapy is started (pre-treatment predictors) or during therapy (on-treatment predictors). Preferably the on-treatment predictors should be available early in the treatment course so that patients who are unlikely to respond can have their treatment stopped and those who are likely to respond can be encouraged to complete therapy. In the following sections we briefly review the predictability of response to treatment in a non-exhaustive manner. Readers are referred to recent reviews[6,7] for more detailed analyses.

Pre-treatment predictors

Regular interferon-based therapies

Several demographic, biochemical, virological and histological predictors of response have been identified from clinical trials of regular interferon-based therapies (Table 1). The two most important parameters are the HCV genotype and pretreatment HCV RNA levels (viral load).[8–12] HCV genotype 1 is the most difficult to treat, whereas genotypes 2 and 3 are the most susceptible to interferon therapy. A low baseline serum viral load (<2 million copies/mL or 800 000 IU/mL) is associated with a significantly higher probability of achieving SVR following interferon-based therapy. SVR rates with interferon + ribavirin combination treatment are increased 1.5-fold after 24 weeks of treatment in patients with <2 million copies/mL, compared with patients with higher viral loads.[8] Other important, albeit less strong factors associated with SVR, include: shorter disease duration, age <40 years, lower body weight, absence of cirrhosis, mild or absent portal fibrosis, low hepatic iron concentration, low HCV genome heterogeneity (quasispecies), gender (women responding better than men) and levels of liver enzymes.[8–12]

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Table 1. Pre-treatment predictors of sustained virological response to various therapies in chronic hepatitis C

	Regular IFN-based regimens[8–12,18]	Peg-IFN monotherapy[13–16]	Peg-IFN α-2b + ribavirin[5]	Peg-IFN α-2a + ribavirin[4]
Low HCV viral load	yes	yes	yes	no
HCV genotype other than 1	yes	yes	yes	yes
Age <40 years	yes	yes	yes	yes
Absence of cirrhosis or fibrosis	yes	yes	yes	no
Low hepatic iron	yes	unknown	unknown	unknown
Low HCV heterogeneity	yes	unknown	unknown	unknown
Female gender	yes	no	no	no
Low body weight	yes	yes	yes	yes
High AST or ALT	yes	yes	no	no
Shorter duration of infection	yes	unknown	unknown	unknown

Superscripts indicate the germane references for each treatment modality. Yes, significant predictor; no, not a significant predictor; IFN, interferon; Peg-IFN, peginterferon; AST, aspartate transaminase; ALT, alanine transaminase.

Pegylated interferons

Two forms of pegylated interferon are currently available, peginterferon α-2a (40 kDa) (Pegasys) and peginterferon α-2b (12 kDa) (Pegintron). Factors predictive of SVR are summarized in Table 1. Non-1 HCV genotype and low viral load were also found to be important predictors of response to both forms of pegylated interferon monotherapy.[13,14] In addition, for peginterferon α-2a, other factors shown to be useful predictors of response include: absence of cirrhosis or bridging fibrosis, body weight <85 kg, body surface area <2 m², age <40 years, alanine aminotransferase levels >3 × ULN (upper limit of normal), and a Knodell histological activity index (HAI) score >10.[14–16] It is interesting that the last two factors are indices of hepatic necroinflammatory activity, suggesting that peginterferon, in contrast to standard interferon or interferon/ribavirin combination therapy, exerts a greater antiviral effect in those with more baseline liver inflammation, which is analogous to antiviral treatment in chronic hepatitis B.[17]

Combination therapy using pegylated interferon and ribavirin is now clearly the gold standard of treatment for chronic hepatitis C. The SVR rates induced by peginterferon + ribavirin therapy differ according to HCV genotype: in genotype 1 patients, 42–51%, and in genotype 2/3 patients, 76–82%. These differential response rates indicate that again HCV genotype is the strongest predictor of sustained response; however, there is a curious difference between the two peginterferons in prognostic implications of viral load.[5]

In patients treated for 48 weeks with two different dosages of pegylated interferon α-2b (1.5 μg/kg or 1.5 μg/kg followed by 0.5 μg/kg) plus ribavirin, a viral load <2 million copies/mL was associated with responses 1.5- to two-fold better than cases with high viral load, whereas genotype 2/3 patients exhibited an approximately two-fold increase in SVR rate compared with genotype 1 patients.[5] Logistic regression analysis demonstrated five baseline variables associated with SVR: genotype non-1, low viral load, lighter body weight, younger age and absence of bridging fibrosis/cirrhosis.

For peginterferon α-2a + ribavirin, only three variables are significantly associated with SVR: genotype non-1, age <40 years and body weight <75 kg.[4] With this form of peginterferon + ribavirin, viral load and presence of significant fibrosis/cirrhosis are not important predictive factors. The reasons for this disparity in predictive response factors between the two types of pegylated interferons remain unclear. In particular, the unimportance of viral load, which is generally the second strongest pre-treatment predictive factor (after genotype) for all other types of pegylated and standard interferons, and combination therapies, is surprising, and defies easy explanation. A type II error is unlikely, as the sample size for the combination peginterferon α-2a/ribavirin study was ~1100 patients. We believe that the underlying explanation is that these two peginterferons are not interchangeably similar, as some have suggested, but rather differ in pharmacodynamics, bioavailability and perhaps antiviral efficacy.

Predictors of response after initiation of therapy

Although pre-treatment predictors are useful in making a general prediction of the efficacy of antiviral therapy, they are not accurate enough in individual patients to make clinical decisions. Most physicians would not withhold treatment based only on pre-treatment parameters. On the other hand, committing a patient to a potentially toxic and expensive therapy for nearly a year with only a small chance of virological response is also undesirable. For this reason, the ability to predict SVR based on biochemical or virological parameters early into therapy has been extensively investigated.

Many studies have conclusively shown that liver chemistry tests such as serum aminotransferase levels are an unreliable predictor of virological response. Although a rapid normalization of serum aminotransferases after starting therapy is often seen in those who go on to achieve SVR, the correlation between this phenomenon and SVR is not high enough to make this a reliable predictor in individual patients.[7] Some preliminary or small studies have suggested the utility of other biochemical markers such as the cytokines tumour necrosis factor α or interleukins as predictive factors but the results to date generally do not show superior results to aminotransferases.[7] Instead, recent studies have indicated that viral kinetics during the early weeks of therapy are likely to be the best predictors of ultimate SVR. In these studies, the concept of early viral response, defined as undetectability or >2 $\log_{10}$ drop from baseline HCV RNA, at an early time point of treatment such as week 4 or week 12, has been validated. The positive predictive values (PPV; the chance of correctly identifying a virological responder) of early viral responses have ranged from ~50% to 80%, i.e. fair to good, whereas the negative predictive values (NPV; chances of correctly identifying a virological non-responder) generally exceeded 90%. Therefore, the decision to continue or stop therapy using early on-treatment prediction criteria has focused on the high NPV, i.e. discontinuing treatment early in those patients who have little or no chance of being a sustained viral responder.

Regular interferon and ribavirin combination therapy

It is sadly probable that non-pegylated interferon + ribavirin therapy will, for economic reasons, continue as the standard treatment for the vast majority of the world's HCV patients, who live in economically underdeveloped countries. Therefore prediction of outcome with this treatment continues to be clinically relevant in most of the world. Based on a seminal paper which showed that a positive HCV RNA test at week 24 of therapy could correctly identify 98% of patients who will not attain SVR,[18] it was routinely recommended to continue therapy in all patients until this time point. However, that study has been criticized for several weaknesses,[19] and alternative strategies may be more cost-effective. Specifically, measurement of viral load decline at week 4, 8 or 12 of therapy may allow much earlier identification of non-responders. In smaller studies, HCV RNA decline at these early time points showed very high NPV.[20,21] Certainly worth examining is the predictability of a week 12 early viral response, which has been shown to have extremely high NPV in the peginterferon trials (see below); this issue could and should be formally tested in the interferon α-2b + ribavirin database.

Pegylated interferons

Even more so than with unmodified interferon, the likely response of an individual patient to peginterferon α-2a can be predicted by an early HCV RNA level. Analyses of the pooled data (814 patients) from three large controlled trials with peginterferon α-2a monotherapy showed that an early viral response after 12 weeks of therapy was the most accurate indicator of SVR when compared with corresponding values obtained at 4, 8 or 24 weeks.[16] In this analysis, it was shown that although the PPVs of such HCV RNA changes ranged between 46% and 77%, the NPV was highest (98%) at the 12 week time period. This means that the decision to continue or stop peginterferon α-2a monotherapy can be made at the 12 week time period.

Recent studies indicate that the early viral response at 12 weeks with combination peginterferon and ribavirin therapy also offers excellent predictability, especially NPV. A recent analysis by Davis,[6] who accessed the combined peginterferon α-2a and α-2b + ribavirin databases, showed that an early viral response at week 12 would result in missing almost none of the non-responders (i.e. 98–99% NPV), and result in cost savings of 16% compared with the strategy of treating all genotype 2/3 patients for 24 weeks and treating all genotype 1 patients for 48 weeks. Thus, as with pegylated interferon monotherapy, the decision to stop or continue therapy for pegylated interferon + ribavirin combination treatment can be made at 12 weeks.

This strategy can be further refined according to the HCV genotype. The week 12 early viral response produces a 98% NPV in genotype 1 patients, so clearly the 12 week stop rule is applicable in this group. In genotype 2/3 patients, 97% show an early viral response, so calculating NPV becomes unreliable because of the minute sample sizes (in the peginterferon α-2a + ribavirin database, only four genotype 2/3 patients did not show an early viral response). Given these considerations, the recent NIH consensus conference recommended, quite appropriately, that genotype 2 and 3 patients simply be treated for 24 weeks without bothering to check week 12 HCV RNA.[6,22]

Future directions

The 12 week stop strategy is effective, but might it be possible to stop therapy even earlier by examining viral kinetics or other factors? Preliminary data indicate that the analysis of the rate of viral decline in serum may offer another means to predict therapeutic outcome with interferon therapy. Rapid viral response (a minimum 2 $\log_{10}$ decline in viral titre in the initial 4 weeks of therapy followed by an additional minimum 2 $\log_{10}$ decline in viral titre until week 8) was a very strong predictor of SVR with an odds ratio of 38.7 in a preliminary study.[23] It may even be possible to use the kinetics of early viral clearance within the first few days to predict treatment outcomes. For example, Magalini *et al.*[24] found that failure to achieve an 85% reduction in HCV RNA level after only 3 days of interferon therapy accurately predicted persistence of viraemia at 4 weeks and correlated with SVR. These studies

were carried out with relatively small sample sizes, so more robust predictability of such extremely early viral kinetics will need verification and validation in much larger studies.

If the week 12 early viral response results in a modest 16% cost savings, the potential cost saving with a week 4 response would be much more impressive, if the predictability parameters were improved. Indeed for peginterferon α-2a monotherapy, the combined PPVs and NPVs were highest for the week 4 early viral response,[16] but the NPV was only 91%, indicating that stopping therapy at this time point would mean that one of every 11 patients who could attain SVR would have their treatment prematurely discontinued. The NPV at week 8 was 95%, so perhaps the week 8 strategy might be the most cost-effective. These different strategies could be subjected to detailed economic analysis by modelling techniques.

Because almost all the Phase 2 and 3 trials of interferon-based therapy were carried out in North American and Western European centres, HCV genotypes 1, 2 and 3 accounted for >95% of the patient sample. Thus, information about predictors, and even SVR rates, in genotype 4, 5 and 6 patients is limited. Moreover, other subgroups under-represented in the clinical trials included Asian and Black patients, as well as those with compensated cirrhosis. For example, peginterferon α-2a + ribavirin in cirrhotic patients using the week 12 early viral response showed a 100% NPV, but this was based on only 56 patients. Both pre-treatment and on-treatment predictive factors in these subgroups clearly require further study.

Acknowledgements

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