All too frequent we physicians ignore “primum non nocere” (first do not harm), and believe all too frequently treatment is always the answer. Once we have treatments available, we frequently believe that the worst which can happen is the failure of treatment, ignoring that side effects might be more than a mere nuisance. Even a supposedly safe treatment such as lamivudine was demonstrated to be lethal in very special individuals with certain viral resistance mutations, when lamivudine was not stopped in time [1]. In contrast to lamivudine and other oral antivirals for hepatitis B, which extremely rarely cause adverse events and seem to have a safety profile similar to placebo [2,3], the current therapy of hepatitis C is both less safe and not effective in everyone.

Interferon has been the backbone of HCV therapy for more than 20 years, but likely will remain a crucial component of HCV treatment regimens only for a few more years.

In the early nineties, only about 5 to 10% of patients sustained normalization of liver enzymes with/without sustained viral response (SVR) after 24 weeks of therapy [4], and still remained below 20% when extended to 48 weeks. A significant improvement was the addition of ribavirin, leading to a significantly and clinically meaningful increase in the rate of SVR, but also to more side effects [5,6].

The modification of the standard interferon molecule by coupling interferon with a polyethylene glycol (PEG) improved the success rates, but did not improve the overall safety profile of HCV targeted therapy, and might have further increased side effects [7,8]. Interestingly, all randomized studies comparing pegylated interferon-α2a to -α2b showed a slight and sometimes significant advantage for PegIFN-α2a [9]. Of note, even the largest trial sponsored by Schering-Plough and producer of PegIFN-α2b demonstrated a 1% difference in favor of PegIFN-α2a [10]. However, while the efficacy was seen to be slightly higher with PegIFN-α2a, the risk of death and serious adverse events (SAE) was likewise slightly higher, suggesting there is indeed "no such thing as a free lunch". A meta-analysis reported 50 deaths in 13,168 patients treated with a PegIFN-α2b containing regimens (0.058% or 1 in 823 [95% CI: 0.033–0.094%]) [11]. Note that the confidence intervals do not overlap, suggesting statistical significant difference in the epidemiologic aspect. Similar results were observed for higher SAE rates in patients receiving regimens containing PegIFN alpha-2a than in those with PegIFN alpha-2b (7.45 vs. 6.74%). This analysis also suggested that the risk of an SAE might be lower with lower doses and shorter duration of therapy. For either PegIFN lower rates of SAE were observed with standard 48-week therapy versus extended duration therapy 6.67% versus 15.5% (sixteen (0.058%; 95% CI 0.033–0.094%) patients).

Therefore, pre-treatment predictors and on treatment prediction of response became crucial: HCV genotype (2-3-4-1 best to worst response), ethnicity (Asians responding best and African Americans the worst, Caucasians and Hispanics in-between), low HCV baseline viral load, younger age, histology (low fibrosis and little or no steatosis), low GGT levels, and more recently IL28B genotype were identified as crucial predictors [8,12,13]. However, only the viral load decline at week 12 would sufficiently distinguish a non-responder from a potential responder [9], to modify treatment with negative predictive value.

It was interesting to note that results for prediction response based on earlier time points than the week 12 results have never been published, until an alternative long-acting interferon coupled to albumin was developed. In that study it was demonstrated that the eventual response or non-response, respectively, could be predicted as early as week 2 in some and at week 4 in others, demonstrating that <1 log at week 4 is similar in predicting eventual failure to achieve SVR as SAE. This analysis also suggested that the risk of an SAE might be lower with lower doses and shorter duration of therapy. For either PegIFN lower rates of SAE were observed with standard 48-week therapy versus extended duration therapy 6.67% versus 15.5% (sixteen (0.058%; 95% CI 0.033–0.094%) patients).

From the licensing of pegylated interferon, it took about a decade until a newer more effective therapy became available in form of the two currently licensed protease inhibitors: boceprevir and telaprevir [15–18]. These treatments have increase SVR rates by roughly 30%.

As with most of the previous improvements in therapy for HCV, either of these protease inhibitors currently licensed, boceprevir and telaprevir, significantly increase rate and severity of adverse events. Though each has distinct side effects, the major concerns are potential fatalities. Thus, for now higher efficacy is gained at the cost of more and potentially fatal side effects [20].
Initially there was a dilemma, how to triage all those patients now in line to be treated [19]. However, quickly after the licensing of the protease inhibitors, amazing data suggesting much easier regimens with even higher success rates are emerging, since autumn 2011, with expected licensing of an easier treatment as early as 2014. The rapid development of direct antiviral agents (DAA) for HCV led Jean Michel Pawlotsky to pronounce, in his summary of “The International Liver Meeting” in April 2012, the foreseeable “death of interferon”.

Interestingly, with each improvement of efficacy concerning HCV clearance, treatments have increased in side effects so far, but that is likely to change with the next round of DAA to be licensed in the near future.

Thus, the major clinical question facing physicians caring for patients with advanced fibrosis in 2013 will be: does the patient need treatment now or is there time to await the very promising newer treatments, and to consider what can be a downside of treatment now?

One concern with unsuccessful therapy is the development of resistance, which can occur against both an antiviral and against interferon. There is no question that antivirals select for mutations associated with resistance [21], and mathematical modelling suggests that resistance development might be successfully be overcome, when a treatment regimen would require 4 or more mutations to lose its effect [22]. Interferon resistance is less accepted, but there are several lines of evidence: in vitro cells can acquire resistance towards interferon when conditioned with interferon [23,24]. This phenomenon can explain why some patients showed less decline of viral load with subsequent improved treatments from standard IFN to pegylated interferon with ribavirin, with each improved treatment viral load decline should have been steeper than in a previous less effective therapy. However, in several patients a less steep decline is observed in subsequent therapies, compatible with resistance to interferon.

Secondary, the concept of interferon resistance would be supported by the data that previously treated patients also respond less to a subsequent treatment with direct antiviral, such as the data presented for ABT-450/R+ABT-333 and GS-7977, respectively, in treatment naïve versus treatment experienced patients [25,26].

Thus, patients with mild to moderate disease (Stage 0 to 2) should most likely be advised to await the newer options, as we likely will see treatments emerging which are effective in almost everyone, with fewer side effects than current treatment.

In contrast, patients with advanced fibrosis (F3) and more so with cirrhosis (F4) will be those with the greatest need for treatment rather sooner than later. Unfortunately, this patient population is usually under-represented in most HCV clinical trials.

The analysis presented in this issue of the Journal of Hepatology highlights the specific information for that population of patients with advanced fibrosis [27]. Though clearly an individual study would be preferential, the retrospective analysis, reported in this issue of the Journal, still gives important additional information. This analysis also gives a clear example of the shortcoming of the small sample size in post hoc analysis, as a higher SVR rate is reported in patients with cirrhosis randomized to the PegIFN RBV arm (6/13, 46%) versus those randomized to PegIFN RBV plus boceprevir arms (5/16, 31% in the response guided therapy arm, and 10/24, 41% in the fixed 48-week therapy arm).

Importantly, patients showing <1 log decline during the “lead-in” with PegIFN had low SVR even in the BOC containing arms with 11–33% for F3 and 10–14% for F4, versus 69% to 89% SVR in those achieving ≥1 log decline by week 4. Thus, for those failing to achieve 1 log decline by week 4 in the lead-in period, there was only a low chance to achieve SVR by adding boceprevir. Because of the numbers in each of the group are small, the prediction has high uncertainty, but certainly warrants critical consideration of risk–benefit ratio. In the subgroup of patients with a baseline viral load >2,000,000 IU/ml, the failure to achieve 1 log reduction resulted in a 94% negative predictive value for achieving SVR; thus giving a relative clear indication to stop therapy if the 1 log decline margin is not crossed [15].

In a similar study with telaprevir, it was likewise seen that patients with ≥1 log decline tended to more likely achieve SVR than those with 1 log decline, during a 4-week “lead-in” period with peginterferon and ribavirin. This difference between those with ≥1 log versus those with 1 log decline was only significant in the previous null-responders with 54% vs. 15%, while the difference was 59% vs. 56% in partial responders (which would be more likely non-responders in the boceprevir study) and 90% vs. 60% in previous relapers, and overall 90% vs. 33% for >1 log versus <1 log in a 4-week “lead-in” with PegIFN and ribavirin [28]. In that study, 40 to 50% of patients had advanced fibrosis, but no separate analysis for F3 and/or F4 fibrosis was given in the telaprevir study. This could potentially suggest that for partial responders with ≥1 log decline, boceprevir might be the better choice, while telaprevir might be the better choice for those with less than 1 log decline. Importantly, there is no head to head study and numbers are too small to gain small confidence intervals to be confident.

In both these recent analyses, about 2/3 of F3/F4 patients with prior relapse or partial response/non-response achieve more than 1 log decline at week 4, which resulted in very good SVR rates of about 80%.

For a 4-week “lead-in” study with PegIFN and ribavirin, prior to adding telaprevir, only a less than 2 log decline at week 12 was highly predictive of failure to achieve SVR [26].

Will IL28B remain relevant with treatments getting more effective and approaching 100%?

Scientifically? Yes! Some interferon-free studies still found a role for IL28B with a direct antiviral alone. Patients with beneficial IL28B genotype might be more likely to qualify for shortened treatment duration, but if such shortened durations are indeed best managed by IL28B or better by on treatment response remains to be determined.

Clinically? Likely not! The importance of IL28B in protease inhibitor plus PegIFN and ribavirin therapy was smaller than in PegIFN plus ribavirin. IL28B is already less likely to determine to start current triple therapy due to the relative high chance of SVR, even in patients with less favorable IL28B genotypes. Furthermore, on treatment response will likely be more important than a pretreatment predictor. In that regard, it is worth noting that in the retrospective analysis of the pivotal boceprevir studies (SPRINT-2, and RESPOND-2) presented in this issue, viral load reduction by more than 1 log at week 4 was the strongest predictor of SVR achievement.

However, with treatment durations approaching a total of 4 weeks, the time point to determine virological on treatment response will be required to be as early as at day 2 or 3 of therapy.

Will we truly cure HCV in 4 weeks? Given the horizon of development in HCV about a decade ago, I predicted in 2005, that in 10 years from then, we will be able to cure HCV in 4 weeks.
This would contradict the mathematical modeling from 2011 that suggested that 7 to 10 weeks would be the minimal duration [29]. However, there are no data to model on what happens between the virus becoming undetectable and when the last virus is eliminated from the body. We have seen already 14 out of 14 patients being negative at SVR4, in a 6-week regimen [30].

Though the treatment duration for the future is still evolving, the close to 100% SVR rate appears to approach reality within the next 3 years, at least for treatment naïve patients. However, cirrhotic patients likely will remain more difficult to treat, and therefore, inclusion of a substantial proportion of cirrhotic patients into ongoing and future phase III studies would be crucial to assess safety and efficacy of newer DAA in cirrhotic patients.

Conflict of interest

Dr. Hans L. Tillmann discloses following conflict of interests: Abbott & AbbVie (employment of my wife and stocks, associated research support in Germany), Gilead (Stocks and Consulting), Biotest, BMS, Merck, Roche (Consulting), Novartis (DSMB), Vertex, Medtronic, Idera, Analays/Roche (Salary support via DCRI).

References


