Tremendous progress has been made in developing effective therapies for hepatitis C. The process began in the mid-1980s with the use of standard interferon for 6 months. The duration of therapy was extended to 12 months. Next, the addition of ribavirin was found to substantially improve rates of sustained virologic response (SVR). More recently, the use of pegylated interferons has largely supplanted standard interferons. More recent efforts have focused on refining the treatment strategy and determining optimal dosing and duration of both peginterferons and ribavirin, leading to the current situation where it is now possible to tailor therapy to the individual patient based on their HCV genotype and their early response during therapy.

Optimal Duration of Therapy

As described above, treatment durations of 24 weeks and then 48 weeks were somewhat arbitrarily determined. One of the first studies to address treatment duration prospectively was reported by Hadziyannis and colleagues (1). In this clinical trial involving 1,311 patients with chronic hepatitis C, subjects were randomly assigned into one of four groups for either 24 or 48 weeks, with either low or standard dose of ribavirin. It was found that among patients infected with HCV genotype 1, 48 weeks of treatment was superior to 24 weeks. SVR rates with 48 weeks of treatment were 52% and 41% for standard and lower dose ribavirin compared to 42% and 29% with 24 weeks of treatment. However, for those infected with genotypes 2 or 3, response rates were comparable between 24 and 48 weeks. Since that time, 24 weeks has been adopted as a standard treatment period for genotype 2 and 3. A subsequent study reported by Zeuzem and colleagues focused exclusively on 124 patients with genotype 2 or 3 treated with peginterferon alfa-2b and weight-based ribavirin (800 to 1,400 mg/day) (2). The SVR rate was higher in patients infected with HCV genotype 2 than those with genotype 3 (93% vs 79%, p=0.020). This study confirmed the adequacy of 24 weeks of treatment, but also pointed out that the response rate was higher with genotype 2 than genotype 3.

There have been several recent studies aimed at determining if the treatment period can be shortened even further for individuals with these more responsive genotypes. Unfortunately, each of these studies has slightly different design features, making them difficult to compare. In three of the studies, assessment of rapid virologic response (i.e. HCV RNA negativity at week 4) was integrated into the study design – essentially only patients with RVR were exposed to the shorter duration of therapy. However, the Accelerate study simply randomized all
patients to either 16 or 24 weeks of therapy; a retrospective analysis was then done according to RVR and these are the data shown in Table 1. This largest of the studies does not support a shorter treatment duration than 24 weeks for patients with HCV genotypes 2 or 3 and is in contrast to the three smaller studies, each of which suggested a comparable outcome for shorter treatment (12, 14 or 16 weeks) and standard treatment (24 weeks), as long as the patient achieved a RVR (6).

It can be concluded then that treatment duration for HCV genotypes 2 and 3 should definitely not be shortened to less than 24 weeks if the patient is still HCV RNA positive after 4 weeks of treatment. Even if the patient does achieve an RVR, 24 weeks of treatment should probably still be considered, but could be shortened with reasonable expectation of success if the patient has intolerable side effects that require discontinuation of therapy.

Assessment of Rapid Virologic Response

It has been apparent for some time now that it is possible to predict early in individual patients what the likely outcome of antiviral therapy for hepatitis C will be. This developed into an assessment of early virologic response, assessed at 12 weeks (7,8). Thus, if at 12 weeks on therapy the patient has not experienced a reduction of serum HCV RNA to undetectable or by at least 2 logs, it is extremely unlikely that they will achieve a sustained virologic response (SVR). More recently, attention has focused on assessment of the rapid virologic response (RVR), defined as undetectable HCV RNA after only 4 weeks of treatment (9,10). A post-hoc analysis by Jensen and colleagues of data from the Hadziyannis study aimed to identify factors associated with a RVR at 4 weeks (9,10). Of 216 patients with HCV genotype 1 treated for 24 weeks, 51 (24%) had a RVR. In summary, they found that 24% of patients with HCV genotype 1 treated with peginterferon alfa-2a and ribavirin sustained an RVR, portending an 89% probability of SVR after 24 weeks of treatment.

These observations led to studies aimed at identifying those patients less likely to have an SVR (i.e. those who not achieve an RVR), and prolonging their therapy. Mathematical modeling suggests that the rate of SVR in patients infected with HCV genotype 1 may correlate with the duration of treatment once HCV RNA has been cleared from serum (14). One of these studies, referred to as the TERAVIC study used the week 4 response as a randomization point (11). Thus 510 patients with chronic hepatitis C infection were treated with peginterferon alfa-2a plus ribavirin (800 mg/d). Those who were still HCV RNA positive after 4 weeks (n=326), were randomized to complete the balance of 48 weeks of treatment or to have treatment extended to a total of 72 weeks. The rate of SVR was significantly higher for those treated for 72 weeks compared to those treated for the standard period of 48 weeks (45% vs. 32%, p<0.003). In contrast, a study which simply randomized patients infected with HCV genotype 1 to either 48 or 72 weeks of treatment was not able to show a significant difference in outcomes (SVR 63% vs 54%) (12). A subgroup analysis of patients from this study found that extended treatment might be beneficial for those patients who had low levels of HCV RNA (but still detectable) at week 12, thus hearkening back to the idea of requiring treatment to maintain HCV RNA undetectability for a minimum period of time (14).

Thus, there is some evidence that prolonged therapy may be beneficial for some patients, but this evidence does not seem compelling enough to introduce this approach into standard therapy, but it might be used on a
case-by-case basis. It does appear that more physicians are incorporating assessment of week 4 response into their management of patients with chronic hepatitis C.

### Management of Nonresponders

Even with optimization or individualization of treatment as described above, 40% to 50% of patients with HCV genotype 1 are not able to achieve an SVR and are therefore at risk of progressive liver disease. Even more frustrating are those who appear to be responding (end of treatment response, ETR) but then relapse. There is no clear strategy for treatment of these patients. Re-treatment appears to be of little benefit, unless the patient was not able to receive full doses of therapy during the initial treatment. Thus, support with better patient education, use if antidepressants or growth factors may allow patients to complete a full course of therapy if initial treatment was curtailed because of side effects.

There is some preliminary evidence that using a different type of interferon for re-treatment may be associated with improved outcomes. Re-treatment with peginterferon alfa-2a of patients who had previously not responded to peginterferon alfa-2b, indicates that a large proportion are able to achieve an EVR when retreated (13). In this study, referred to as the REPEAT study, 950 non-responders to peginterferon alfa-2b were randomized to receive either standard dosing of peginterferon alfa-2a (180 mg/wk) or an induction dose (360 mg/wk). Those receiving the induction had a higher rate of HCV RNA reductions to negative or by at least 2 logs at 12 weeks (62% vs 45%). Treatment is ongoing and no information is yet available on SVR rates in these patients.

An open label pilot study of 24 chronic hepatitis C outpatient non-responders to (12 cases), or relapsers after (12 cases), standard combination therapy were treated with consensus interferon (9 μg five times per week) for 36 weeks. The patients were followed up for a further 24 weeks. The primary end-point of the study was the rate of sustained virological response. SVR occurred in 33% of previous non-responders and in 42% of previous relapsers (15). This was followed by the DIRECT Trial (Daily-dose consensus Interferon and Ribavirin Efficacy of Combined Therapy from which only preliminary results are available (16). This was a large, multicenter, randomized trial in more than 500 patients who had previously failed to achieve an SVR with pegylated interferon plus ribavirin. They were randomized to receive one of two doses of consensus interferon combined with ribavirin (1,000 to 1,200 mg/day). Group 1 received 9 μg/day, group 2 received 15 μg/day and a third group received no treatment, with the intention to randomize patients in the no-treatment group to 1 of the 2 active treatment groups at 6 months if the DIRECT trial showed positive results. The interim analysis evaluated on treatment responses which were approximately 25% at 48 weeks, with some SVRs noted.

There has also been considerable interest in the approach of long-term maintenance therapy using lower than standard doses of peginterferon in patients who had previously not responded to therapy. Although no conclusive data are yet available, at least three studies testing this idea are underway, referred to as the HALT-C Trial, The CO-PILOT study and the EPIC3 study. In the HALT-C Trial, 1050 patients who had failed to achieve an SVR to standard interferon with or without ribavirin and did not respond to re-treatment with pegylated interferon and ribavirin were randomized to receive either low dose pegylated interferon (90 μg/week) or to remain untreated for a total of 42 weeks. Outcomes being assessed in this and the other trials of maintenance therapy are development of clinical features of liver failure or hepatocellular carcinoma.
There is also considerable interest in the use of new small molecule antiviral agents for treatment of interferon non-responders. These agents generally fall into one of two categories – protease or polymerase inhibitors. Preliminary studies show that several of these agents (including telaprevir and valopicitabine) are able to induce significant reductions in serum levels of HCV RNA, even in interferon non-responders. It is apparent though that emergence of viral resistance is a significant clinical problem in patients treated with some antivirals such as telaprevir. It is likely that this will be an issue with all protease and polymerase inhibitors. Studies are ongoing to determine how best to use these agents (optimal duration, whether they need to be combined with peginterferon and/or ribavirin, dosing etc).

**Conclusions**

We have made considerable progress in developing effective treatments against HCV. Patients infected with HCV genotypes 2 and 3 have very high rates of response and seem to need less intensive treatment than those with genotype 1. For the latter, we now have a much clearer understanding of how to monitor and tailor therapy. We look forward to the availability of new direct antivirals as a means to effectively manage a much greater proportion of individuals infected with HCV.

It is likely that in the future we will be able to tailor therapy to individual patients. Because they respond well to pegylated interferon and ribavirin, patients infected with HCV genotype 2 or 3 will be treated with these agents first, with the goal of achieving 24 weeks of treatment and the understanding that 12 weeks might be acceptable in certain individuals. Until the role of small molecule antiviral is better defined, it is likely that pegylated interferon and ribavirin will remain the mainstays of treatment of HCV genotype 1 infection too. It is already clear that treatment can be discontinued as early as 12 weeks into therapy of the patients does not achieve an EVR. It is likely that future studies will help to clarify the role of extended treatment (beyond 48 weeks) in certain individuals with a less than optimal early response.

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