Review

Optimizing outcomes in patients with hepatitis C virus genotype 2 or 3

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Introduction

As Lee and Ferenci [1] discuss elsewhere in this supplement, it is no longer appropriate to generalize that patients with hepatitis C virus (HCV) genotype 1 and 4 are ‘difficult to cure’, because of viral kinetic evidence to the contrary. Conversely, it is no longer appropriate to think of all patients with HCV genotype 2 or 3 as ‘easy to cure’, because of the importance of early virological response (EVR) as a predictor of response in genotype 2 or 3 patients, as it is achieved by 97% of this population. However, rapid virological response (RVR) measured at week 4 is a strong predictor of sustained virological response (SVR) in this group, and patients achieving an RVR may be suitable candidates for shorter treatment durations. Several small studies investigating the efficacy of shortened treatment durations in this population have been published; however, differences in study design have made their collective interpretation difficult. We discuss these studies, followed by a comparison of the data from ACCELERATE, the largest, randomized trial carried out to investigate abbreviated therapy in genotype 2 and 3 patients. The data confirm that RVR, and its use alongside significant baseline predictors, can assist in optimizing therapy. Patients achieving an RVR have high SVR rates and might be candidates for shorter treatment duration, particularly those displaying a low viral load at baseline; however, the need to consider the increased rate of relapse versus the benefits of abbreviated therapy must also be considered. Conversely, in patients who do not achieve an RVR there is evidence to suggest they may benefit from intensified therapy (longer therapy and/or increased doses). As in genotype 1 and 4 patients, response-guided therapy aims to optimize treatment outcomes for individuals, without compromising SVR rates.
(40 kDa) (Pegasys®; Roche, Basel, Switzerland) plus ribavirin (Copegus®; Roche) at a dose of either 800 mg/day or a weight-based 1,000/1,200 mg/day [7]. SVR rates ranged from 79–84% across the four treatment groups in this trial, with no significant differences between any combination of treatment duration and ribavirin dose [7].

The finding that maximal SVR rates could be obtained with 24 weeks of treatment has spurred researchers to investigate even shorter durations of treatment for patients infected with HCV genotypes 2 or 3. Abbreviated regimens would be less expensive and more convenient, and might have tolerability advantages over the standard 24-week regimen. To date, five trials have examined abbreviated 12–16-week treatment regimens for genotype 2 and 3 [3,8–11]. The various trials differ greatly in study design; thus, great care is necessary when examining the results, especially when attempting to compare results of studies or generalize the findings to a broad population.

An overview of the study design features of the five trials is presented in Table 1. The duration of treatment in the abbreviated regimen varied across trials from 12–16 weeks, but it was how patients were assigned to abbreviated treatment that had the greatest effect on the final SVR rates. In three of the trials, treatment duration was determined on the basis of RVR status at week 4 [8–10]. In contrast, the other two studies randomized patients at baseline to abbreviated treatment or the standard 24-week duration [3,11]. Given what is known about the influence of RVR on SVR rates, it is clear that studies which pre-selected patients with an RVR for abbreviated treatment would produce higher SVR rates than those that did not pre-select patients with favourable characteristics. This is exactly what has been reported.

A shorter treatment duration for those who are fast to respond

The merits of abbreviated therapy can be explored by thorough consideration of the results of two studies: one that assigned patients to abbreviated therapy on the basis of RVR status [9], and a second, larger trial (ACCELERATE) that randomized patients at baseline to an abbreviated regimen or the standard duration of therapy [3]. Mangia et al. [9] randomized 283 patients with HCV genotype 2 or 3 to a standard 24-week regimen or a variable treatment duration (12 or 24 weeks) with PEG-IFN-α2b (12 kDa; PegIntron®; Schering-Plough Corporation, Kenilworth, NJ, USA) 1.0 µg/kg/week plus ribavirin 1,000 or 1,200 mg/day. Patients randomized to the variable regimen were assigned at week 4 on the basis of their RVR status to complete a total of either 12 or 24 weeks of treatment. As might be expected, the highest SVR rate in the variable duration group was obtained in patients with an RVR who were assigned to 12 weeks of treatment (85% versus 64% in those patients without an RVR treated for 24 weeks; Figure 1). The overall SVR rate in the group randomized at baseline to 24 weeks of treatment was 76% [9].

When overall SVR rates are computed for the two groups, there is seemingly little difference between them: 76% of patients randomized to the standard 24-week duration of treatment and 77% in those randomized to the variable regimen with treatment duration based on RVR. On this basis, the variable duration strategy appears to be a reasonable alternative to the standard 24-week regimen; however, a more careful inspection of the data reveals a potential drawback of abbreviated therapy – genotype 2 or 3

<table>
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HCV, hepatitis C virus; PEG-IFN-α2a, pegylated interferon-α2a; PEG-IFN-α2b, pegylated interferon-α2b; RBV, ribavirin; RVR, rapid virological response.
patients treated with abbreviated regimens are more likely to experience virological relapse compared with those treated for the standard duration. When only patients with an RVR are considered, the relapse rate was considerably lower in patients randomized to 24 weeks of treatment (2%) than in patients assigned to 12 weeks in the variable duration group (11%; Figure 1) [9]. More patients randomized to the 24-week group withdrew from treatment than in the abbreviated treatment group. Thus, the higher relapse rates in the abbreviated treatment group and the higher dropout rates in the standard group tend to cancel each other out and create the appearance that outcomes are similar in both strategies.

The largest trial to examine the merits of abbreviated therapy in patients with HCV genotype 2 or 3 infection was ACCELERATE, which randomized 1,469 patients at baseline to either 16 or 24 weeks of treatment with PEG-IFN-α2a 180 μg/week plus ribavirin 800 mg/day [3].

Patients with major protocol deviations or <80% exposure to medication were excluded from the protocol-planned primary analysis. In this standard analysis, the SVR rate in patients randomized to 24 weeks of treatment was significantly greater than in those randomized to 16 weeks of treatment (76% versus 65%; odds ratio 0.59, 95% confidence interval 0.46–0.76; P<0.001). The results of an intent-to-treat analysis were consistent with the pre-specified analysis: SVR rates were 70% versus 62% for 24 weeks versus 16 weeks, respectively (odds ratio 0.67, 95% confidence interval 0.54–0.84; P<0.001) [3]. These findings were obtained despite a higher rate of withdrawal in patients randomized to 24 weeks compared with 16 weeks of treatment.

What do the results of ACCELERATE tell us about the management of HCV genotype 2 or 3 infection? The findings demonstrate conclusively that it is not appropriate to recommend abbreviated treatment as a general strategy for patients with genotype 2 or 3 infection [3]. On the surface, this seems to contradict the findings of the trial by Mangia et al. [9]. However, closer inspection of data from ACCELERATE confirms that RVR is a powerful predictor of outcomes in patients with HCV genotype 2 or 3, and also sheds light on the appropriateness of assigning patients to abbreviated treatment based on their RVR status [3].

Two thirds (67%) of all treated patients achieved an RVR in ACCELERATE. Consistent with the overall results of the trial, the SVR rate in patients with an RVR who were treated for 24 weeks was higher (90%) than in patients treated for 16 weeks (82%; Figure 2). The SVR rates were considerably lower in patients without an RVR (49% in patients treated for 24 weeks versus 27% in patients treated for 16 weeks).

When baseline HCV RNA levels are superimposed on RVR, it is apparent that these two factors exert a powerful influence on SVR rates. Although, as shown in Figure 2, treatment for 24 weeks produces consistently higher SVR rates than an abbreviated 16-week regimen, regardless of baseline HCV RNA levels. In patients with low HCV RNA levels, defined as ≤400,000 IU/ml, the SVR rate was 95% in those treated for 24 weeks and 90% in those treated for 16 weeks in ACCELERATE (Figure 3). In contrast, SVR rates were 88% in patients with a baseline HCV RNA level of >800,000 IU/ml who were treated for 24 weeks and 78% in patients treated for 16 weeks. It is also clear that the absolute difference in SVR rates between patients with high and low baseline HCV RNA levels is greater in patients randomized to abbreviated therapy (12% versus 7% in those randomized to 24 weeks).
As stated above, most genotype 2 or 3 patients achieve an EVR. An interesting trend is observed when outcomes are compared in patients based on the time at which an individual becomes HCV RNA negative. Among patients who become HCV RNA negative by week 4 (RVR) or by week 12 (complete EVR), the end of treatment (EOT) virological response rate was almost identical (95% and 94%, respectively). However, relapse is unusual in patients with an RVR and is more common in those who do not become HCV RNA negative until week 12. Thus, SVR rates in these groups are divergent: 90% in those with an RVR and 57% in those with a complete EVR. This is reminiscent of what is observed in patients infected with HCV genotype 1 (see article by Lee and Ferenci in this supplement [1]). Genotype 1 patients with a partial EVR have much lower SVR rates (27%) than patients who have an RVR (87%) or a complete EVR (68%) because of higher relapse rates during follow-up.

**Differences between HCV genotypes 2 and 3**

There were differences in the virological response rates between patients infected with genotypes 2 and 3 in ACCELERATE [3]. Among patients treated for 24 weeks in the intent-to-treat population, those infected with HCV genotype 2 had a higher RVR rate (69% versus 59%), EVR rate (94% versus 85%), EOT response rate (84% versus 80%) and SVR rate (75% versus 66%) as compared with patients infected with HCV genotype 3. The trend was similar in patients randomized to 16 weeks of treatment, although the SVR rate was identical in patients with genotype 2 and 3 (62%).

Among patients with an RVR, the SVR rates were identical in patients with genotype 2 and 3 randomized to 24 weeks of treatment (85%) and similar in those randomized to 16 weeks of treatment (78% in genotype 2 versus 80% in genotype 3). The greatest difference between genotypes was among patients without an RVR who were randomized to 24 weeks of treatment: the SVR rate was 53% in those with genotype 2 and 39% in those with genotype 3 [3]. Mangia et al. [9] also observed differences in the SVR rate between patients infected with genotype 2 and 3. The overall SVR rate was 80% in patients infected with genotype 2 and 66% in patients infected with genotype 3 (P<0.001). As the SVR rate was identical (76%) in genotype 2 and 3 patients randomized to the standard 24-week regimen, this difference was driven entirely by the difference in SVR rates in patients randomized to the variable duration regimen (82% in genotype 2 versus 62% in genotype 3).

High baseline HCV RNA levels have a marked effect on SVR rates in patients infected with genotype 3. This trend has been observed in several trials that have examined abbreviated therapy and is particularly evident in patients treated with abbreviated regimens [3,8,10].
The effect of ribavirin dose

An issue of interest is whether ribavirin dose increases SVR rates in patients receiving abbreviated regimens (the issue of ribavirin dose in the era of response-guided therapy will be discussed in greater detail by Dusheiko et al. [12] in a subsequent article in this supplement). The recommended dose of ribavirin in genotype 2 or 3 patients is a fixed dose of 800 mg/day, which was decided on the basis of the results of a large pivotal trial by Hadziyannis et al. [7]. There was no significant difference in SVR rates in HCV genotype 2 or 3 patients treated for 24 weeks (or 48 weeks) with 800 mg/day or 1,000/1,200 mg/day ribavirin. This indicates that the dose of ribavirin is less important in patients infected with HCV genotypes 2 or 3 than genotypes 1 or 4. It might even be possible to reduce the dose further in patients receiving the standard 24-week regimen [13].

Several trials of abbreviated therapy have used higher doses of ribavirin (800–1,400 mg/day) [8–11], but the use of a higher dose of ribavirin in these trials was empirical. The lack of a control group with a different dose of ribavirin in these trials makes it impossible to tell if the higher dose actually improved outcomes.

Although ACCELERATE used a fixed 800 mg/day dose of ribavirin, the results could shed light on the importance of ribavirin dose with abbreviated regimens. There was a benefit from higher ribavirin exposure in both patients with and without an RVR when they received <17 doses PEG-IFN-α2a. However, when the number of PEG-IFN-α2a doses was >17, ribavirin exposure did not significantly contribute to SVR in patients with or without an RVR [14].

Further study is needed to confirm the optimal ribavirin dose in genotype 2 or 3 patients receiving a shorter treatment duration.

Extending treatment duration in those who are slow to respond

There are data from randomized prospective trials which show that prolonging the duration of treatment increases SVR rates in genotype 1 patients who are slow responders [15,16] (see the article by Ferenci and Lee [1] in this supplement). This raises the question of whether intensification of treatment could increase SVR rates in genotype 2 or 3 patients who do not achieve an RVR. No data from prospective trials are available on this topic; however, this question has been addressed through a retrospective analysis of data [17] from the trial by Hadziyannis et al. [7]. SVR rates ranged from 65–76% across the four treatment groups in this trial (Figure 4). Consistent with results observed in genotype 1 patients, relapse rates decreased in inverse proportion to the intensity of treatment, and were lowest in those treated for 48 weeks with PEG-IFN-α2a plus ribavirin 1,000/1,200 mg/day (4%) and highest in those treated for 24 weeks with PEG-IFN-α2a plus ribavirin 800 mg/day (26%) [17]. Although these results must be confirmed in a prospective study, they suggest that intensification of therapy may be effective in increasing SVR rates in genotype 2 or 3 patients who do not achieve an RVR at week 4.

Conclusion

In conclusion, available data from ACCELERATE and smaller studies demonstrate that genotype 2 or 3 patients with an RVR can achieve high SVR rates with abbreviated therapy. There is a trade off between slightly higher relapse rates in patients treated with abbreviated regimens and slightly higher withdrawal rates in those treated for the standard duration. A higher ribavirin dose in patients who receive a shorter duration might reduce relapse, but this requires further study, as does the strategy of extending the treatment duration to 48 weeks in patients without an RVR at week 4. The highest SVR rates and lowest relapse rates are obtained in patients with an RVR who have low baseline HCV RNA levels (≤400,000 IU/ml). The PROPHESYS cohort may provide further information on the importance of ribavirin dose with abbreviated regimens.
further insight into the potential for response-guided therapy in this population.

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References