When treating an infectious disease dosage and treatment duration are relevant, besides the selection of an appropriate specific drug, for the eradication of the causal living organism. In the case of chronic infection with hepatitis C virus, a number of consensus meetings have clearly established both the dosage and administration time for these drugs. Regarding time, it has been validated that the treatment of infection with hepatitis C virus, genotypes 2 and 3, should last 24 weeks, whereas 48 weeks have been established for genotypes 1 and 4 (1,2). These differences in time according to genotype are accounted for by a faster fall of viral load for genotypes 2 and 3 when using the same doses. This faster response basically results from differences in the C virus NS5a region, which give rise to varying inactivation rates for PKR, a basic component of interferon activity (3).

Based on the individually tailored therapy concept, whether the established treatment duration is necessary for all patients (3-5), and whether a longer duration would result in higher sustained response rates has been questioned (6).

If not resulting in lower effectiveness, a shorter treatment would entail a shorter duration of side effects and lower financial costs, but could also determine a higher number of transient responses. Regarding the former point, i.e., the number and severity of side effects, a shorter therapy will at least result in fewer discontinuations from serious adverse events even if side effects are not significantly reduced. As regards the economic issue, it is clear that the financial burden will be significantly reduced given the price tags for pegylated interferon and ribavirin. However, a shorter treatment course should entail no loss in effectiveness.

**SHORTER THERAPIES**

As different therapy duration has been established for the various genotypes, each virus C genotype will be discussed separately.

**Shorter therapies for genotypes 2 and 3**

The efficacy analysis for genotypes 2 and 3 should not be considered jointly, as standard 24-week therapy is more effective for genotype 2 versus 3 (7). Hence an analysis of the various studies should consider genotypes separately.

Several randomized studies of shorter versus standard therapies have been reported for genotypes 2 and 3, their characteristics being summarized in table I.

Studies reported thus far first reveal that patients who become negative for HVC-RNA within the first month of a 14-week therapy do respond better than non-responders to 24 weeks of treatment, which may be demonstrated for genotypes 2 and 3, and either high or low viral loads (14) (Fig. 1). When patients with negative RNA at week 4 during a 16-week therapy are compared to patients on a...
24-week therapy no differences are seen for genotype 2 cases with high or low viral loads, and for genotype 3 cases with a low viral load, but patients with genotype 3 and a high viral load (> 800,000 IU/ml) respond significantly more to 24 weeks than 16 weeks of treatment (9) (Fig. 2). The latest study assessing response in RNA-patients at week 4 was reported by Mangia (8), who assessed short (12 weeks) and long (24 weeks) therapies using pegylated interferon 2b doses of 1 µg/kg/week. As in the previous study, results also demonstrate no differences between short and long treatment durations for genotype 2, but do show such differences with higher sustained response for genotype 3 (Fig. 3).

Regarding studies with randomization at baseline rather than at negativity in the 4th week, fixed ribavirin doses of 800 mg/day, patients with 24-week regimens exhibit a significantly higher number of sustained viral responses both for genotype 2 (Fig. 4) and genotype 3 (Fig. 5) when compared to subjects on 16-week therapies (10,12), and such differences are maintained in patients who become RNA- at week 4 (10) (Fig. 6). However, when ribavirin doses are weight-adjusted (13) no significant differences occur for genotype 2. The importance of ribavirin doses may be also seen in genotypes 2 and 3 on 24-week regimens (15).

Thus, from all the above it may be recommended, even if data are insufficient to unequivocally establish such recommendation, that therapy in patients who become negative for HVC-RNA at week 4 be shortened, always using ribavirin weight-adjusted doses, and particularly when viral loads are low (< 600,000 IU/ml) and/or viral genotype is 2. A shorter treatment may be not recommended in cases with sustained response-reducing factors such as high-grade fibrosis, steatosis, or insulin resistance.

### Table I. Shorter therapy randomized studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>No.</th>
<th>Duration</th>
<th>Genotype</th>
<th>Ribavirin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mangia (8)</td>
<td>Per RNA – 4th wk</td>
<td>133/150</td>
<td>12 wks/24 wks</td>
<td>75% G2 and 25% G3</td>
<td>1,000-1,200 mg/day</td>
</tr>
<tr>
<td>Von Wagner (9)</td>
<td>Per RNA – 4th wk</td>
<td>71/71</td>
<td>16 wks/24 wks</td>
<td>38% G2 and 62% G3</td>
<td>800-1,200 mg/day</td>
</tr>
<tr>
<td>Shiffman (10)</td>
<td>At baseline</td>
<td>736/733</td>
<td>16 wks/24 wks</td>
<td>50% G2 and 50% G3</td>
<td>800 mg/day</td>
</tr>
<tr>
<td>Dalgard (11)</td>
<td>Not randomized</td>
<td>95/27</td>
<td>14 wks/24 wks</td>
<td>22% G2 and 78% G3</td>
<td>800-1,400 mg/day</td>
</tr>
<tr>
<td>Lagging (12)</td>
<td>At baseline</td>
<td>170/170</td>
<td>12 wks/24 wks</td>
<td>50% G2 and 50% G3</td>
<td>800 mg/day</td>
</tr>
<tr>
<td>Yu (13)</td>
<td>At baseline</td>
<td>50/100</td>
<td>16 wks/24 wks</td>
<td>100% G2</td>
<td>1,000-1,200 mg/day</td>
</tr>
</tbody>
</table>

Fig. 1. Sustained viral response in the non-randomized study by Dalgard (2004) per genotype and high (HVL) or low (LVL) viral load. Number of cases in each group at the base of each column.

Fig. 2. Sustained viral response in the study by Wagner (2005) per genotype and high (HVL) or low (LVL) viral load. Number of cases in each group at the base of each column.

Fig. 3. Sustained viral response in the study by Wagner (2005) per genotype and high (HVL) or low (LVL) viral load. Number of cases in each group at the base of each column.

### Shorter therapies for genotype 1

Two studies (16,17) (Figs. 7 and 8) analyzed this possibility, and showed that in patients with viral load <
600,000 IU/ml receiving weight-adjusted ribavirin and becoming RNA-negative at week 4 a 24-week regimen is as effective as a 48-week therapy. Conditions for this include that HCV-RNA is measured using a sensitive technique (detection above 25 IU/ml), weight-adjusted ribavirin dosing is used, and no factors negative for sustained viral response are present.

Fig. 3. Sustained viral response in the study by Mangia (2005) per genotype, treatment duration, and RNA negativization at week 4. Number of cases in each group indicated at the top of each column.

Fig. 4. Results for genotype 2 from baseline randomized studies per treatment duration. Number of cases in each group at the base of columns.

Fig. 5. Results for genotype 3 in baseline randomized trials per treatment duration.

Fig. 6. Results from studies by Shiffman (2007) according to time to RNA negativization (< 50 IU/ml) (Shiffman. N Engl J Med 2007; 357: 124).

LONGER THERAPIES

A therapy course longer than established by consensus meetings results in higher costs, and a greater potential for potentially longer side effects, which leads to increased dropouts. These negative aspects must be compensated for by a higher number of sustained viral responses.

Longer therapies for genotypes 2 and 3

Two studies have been reported as abstracts, which analyze such possibility for these genotypes. In one Brown
(15) finds no differences for genotypes 2 and 3, or according to high or low viral loads, between 24- and 48-week regimens, as previously established by pegylated interferons 2a and 2b registry trials. EASL 2007 has been recently presented and reported as an abstract (18); this study compared response to a 24-week regimen vs. a 48-week regimen in patients with genotypes 2 and 3 who remained RNA-positive at week 4, and according to ribavirin doses. In patients with genotype 2 or 3 lacking early viral response therapy for 48 weeks is more effective (65 vs. 76%) provided that weight-adjusted ribavirin doses are used. Unpublished data from both studies are somewhat conflicting, but according to guidelines recommending tailored therapies for patients with no early response, and keeping weight-adjusted ribavirin doses, a longer therapy tends to provide better results. Larger studies are needed to establish this therapy modification as an evidence-based approach.

**Longer therapies for genotype 1**

We are currently aware that treatment for genotype 1 is acceptable, but the overall response rate does not go beyond 50%, hence prolonged treatment may be a theoretically effective option. The problem lies in identifying which patients with genotype 1, initially or based on early virological response, may benefit from prolonged treatment.

This option has been assessed in 3 studies (19-22). A summary of these studies is shown in table II.

These three studies reveal that patients with slow viral response may benefit from prolonged therapy. An analysis of the various studies again shows the significance of ribavirin dosing, as in the studies by Sánchez-Tapias (20,21) and Berg (22) (Fig. 9), with fixed ribavirin doses of 800 mg/day, improved response was seen in patients becoming RNA-negative after week 12, while in the study by Mangia (21) (Fig. 10) ribavirin doses were of 1,000-1,200 mg/day. Such improved response with a 72-week regimen is only seen for patients becoming RNA-negative between weeks 8 and 12. Therefore, while the slow responder concept is difficult to establish, these are basically patients that become negative between weeks 8 and 24, and for whom prolonged, 72-week therapies may result in a higher rate of sustained viral response (23).

**TAILORED TREATMENT AS A FUNCTION OF TIME**

The last few years have shown that therapy for chronic hepatitis C virus infection must be tailored according to individual characteristics and viral load behavior in the first few weeks. We already described how the relevance of virological response at week 4 determined no efficacy loss in shorter regimens. As a result, therapy outcomes for a series of patients with chronic hepatitis C virus infection, genotype 1, have been recently reported (22) as
an abstract. Two groups are established: one was treated for 48 weeks; in the other group treatment duration was adjusted to the week when HCV-RNA became negative—the number of weeks on treatment was defined by multiplying the negativization week number by 6. Result comparisons between 48-week and variable-duration regimens show significant differences favoring the former option (48 versus 34% of sustained viral responses). An individualized analysis of patients showed a decreasing response percentage depending on therapy duration, which seems to question this tailored regimen, at least according to this information.

**CONCLUSIONS**

Enough information seemingly exists to suggest that therapy may be shortened for selected patients, with ribavirin dosing being always adjusted to patient weight. The risk of transient response is minimized—if these patients are re-treated for a standard duration, the rate of sustained responses is almost 100%. Therefore, selecting a shorter regimen for a patient is an individual decision to be based on patient characteristics and the development of virological response at week 4, which seems determinant. Treatment tolerability should also be considered.

Prolonging therapy for treatment-experienced patients with a high percentage of transient responses is much more questionable since results are unclear and efficacy is doubtful; however, in order to provide maximal effectiveness and to minimize transient responses, this may be an effective therapy option on an individual basis.

**REFERENCES**


