Tailoring the length of antiviral treatment for hepatitis C

Alessandra Mangia and Angelo Andriulli

Gut 2010 59: 1-5
doi: 10.1136/gut.2009.179606

Updated information and services can be found at:
http://gut.bmj.com/content/59/01/1.full.html

These include:

References
This article cites 36 articles, 5 of which can be accessed free at:
http://gut.bmj.com/content/59/01/1.full.html#ref-list-1

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To order reprints of this article go to:
http://gut.bmj.com/cgi/reprintform

To subscribe to Gut go to:
http://gut.bmj.com/subscriptions
Tailoring the length of antiviral treatment for hepatitis C

Alessandra Mangia,1 Angelo Andriulli2

The effectiveness of interferon in blocking the replication of hepatitis C virus (HCV) in infected cells is enhanced in patients with genotypes 2 and 3 as compared to genotype 1.1,2 The clinical counterpart of these experimental observations is the higher rate of viral clearance in easy-to-cure genotypes, as reported in registration trials on Peg-Interferon (Peg-IFN) and ribavirin therapy.3–6 Consequently, so far, HCV genotyping has represented the common approach to tailoring drug dosage and length of therapy. Recently, an innovative concept has emerged which might also govern treatment schedules besides HCV genotypes: in response to a single interferon injection, viral decline in blood differs not only among individual genotypes but also from patient to patient infected by the same viral strain.3–6 This evidence has led to the claim that patients with prompt response could benefit from a shorter duration of treatment compared to that which is currently recommended, whereas for slower responders a prolonged course of treatment might be needed to maximise virological response.

How to categorise rapid, slow or null responders according to current antiviral therapy is a matter of intensive investigation.7–15 Past experience has corroborated the usefulness of evaluating serum HCV-RNA at treatment weeks 4, 12 and 24: rapid responders are patients who are non-viraemic at week 4, and non-responders are those still viraemic at week 24; all other patients falling between these two extremes are defined as slow responders.11,12 As the timing and magnitude of virological response are highly variable from one patient to another, slow responders might include several subgroups of patients with differing chances of achieving a sustained virological response (SVR). Indeed, if a subset of patients defined as complete early virological responders shows an absence of HCV-RNA at treatment week 12, it is likely that some of these patients would clear the virus by week 8 and need to be differentiated from those with viral clearance at week 12.15 A third subgroup refers to patients who achieve a ≥2 log decrement in viraemia at week 12, the so-called partial early virological responders. This threshold level of viraemia decline seems arbitrary as it has never been validated by sound pharmacokinetic and pharmacodynamic data.

We suggest that the use of descriptive terms (such as rapid, complete and partial early response, or late response) ceases and more rigorous terminology is used which takes into account the timing of the first undetectable HCV-RNA in the blood. By so doing, viral clearance becomes the basic relevant parameter rather than any arbitrary threshold of viral load decline, and patients would be categorised accordingly as week 4 responders (wk4-R), week 8 responders (wk8-R), week 12 responders (wk12-R), and so on.

The present review will focus on clinical trials that individualise treatment duration in patients with chronic hepatitis C.

SHORTENED TREATMENT DURATION IN PATIENTS WITH TREATMENT WEEK 4 VIRAL CLEARANCE

Plentiful evidence supports the week 4 response (wk4-R) as the primary determinant of treatment duration and response for both patients with easy- and difficult-to-cure genotypes.

Genotype 1

In patients with genotype 1 and wk4-R, the claim that 24 weeks of therapy could be as effective as the recommended 48 weeks treatment duration has been substantiated by several studies (table I). Zeuzem et al.16 have treated low viraemic (<600 000 IU/ml) patients with Peg-IFNα-2b and weight-based ribavirin for 24 weeks: SVR rate was 89% for those with wk4-R, 25% and 17% for patients with wk12-R or wk24-R.16 In secondary analysis of a randomised phase III study on Peg-IFNα-2a and weight-based ribavirin, a wk4-R was reported in 24% of patients, and this predicted either an 89% probability of an SVR after 24 weeks of therapy and a low (9%) relapse rate during the follow-up.17

More compelling data have been presented in two studies from Taiwan which randomised patients with genotype 1 to 24 or 48 weeks of combination therapy with Peg-IFNα-2a and ribavirin (1000–1200 mg/day). Overall, the 48-week arm had significantly better SVR rates than the 24-week arm: rates of 79% versus 59% in the trial by Yu et al.18 and 76% versus 56% in the study by Liu et al.19 were obtained. When SVR was analysed by rapid virological response (RVR), Yu et al.18 reported 100% and 89% rates after 48 and 24 weeks, respectively. However, in patients with low baseline viraemia and wk4-R, SVR rates were comparable with the 48-week and 24-week course of therapy: 100% versus 96.4% in the trial by Yu et al.18 and 100% versus 94% in the trial by Liu et al.19 In contrast, among patients without wk-4R, therapy for 48 weeks was associated with a significantly higher SVR rate than for 24 weeks: 63.8% versus 34.5%, and 39% versus 16%. Finally, two European studies allocated patients to a treatment duration depending on the time of first undetectable HCV-RNA levels: 26% and 29% of enrolled patients attained a wk4-R and received therapy for 24 weeks: SVR rates were 78.8% and 77%.15 In both trials low viraemia levels (<400 000 IU/ml) were determinant of wk4-R, and further predictors were the absence of cirrhosis, low body mass index (BMI), and young age.15 In a study by Berg and colleagues, patients were randomised to either Peg-IFNα-2b and a weight-based ribavirin dosage for 48 weeks or an individualised treatment duration calculated according to the time required to first obtain HCV-RNA negativity, multiplied by the factor of 6. When HCV-RNA negative values were ascertained by using qualitative transcription-mediated amplification assay (TMA; sensitivity limit, 5.3 IU/ml), the overall SVR rates were in favour of the fixed treatment schedule. However, patients with low viraemia (<800 000 IU/ml) and wk4-R achieved comparable SVR rates: 93.3% after 48 weeks and 90.4% after 18–24 weeks of therapy.20

These studies should be sufficient to persuade clinicians to offer a short course of treatment to a subset of patients infected with genotype 1; about one third of patients with low baseline viraemia will show a wk4-R and attain high rates of SVR after 24 weeks of therapy, placing them in the “easy-to-cure” category.
prospect of shorter treatment is appealing for these patients, because the overall tolerability is likely to be better. However, the relapse rate will only be acceptable when short therapy is adopted in patients with low-baseline viraemia. What threshold of serum HCV-RNA should be taken for a low level is debated, yet preliminary observations suggest that levels <200 000 IU/ml are more likely associated with both wk4-R and SVR than levels ranging between 200 000 and 600 000 IU/ml.3,14 Furthermore, as proportions of patients with wk4-R vary widely from one study to the other, further factors might also affect the occurrence of the wk4-R, beside interferon sensitiveness.

Genotypes 2 and 3

Two thirds of patients with genotypes 2 and 3 will clear the virus at treatment week 4,20–24 and this will more likely occur in patients of young age and with mild liver fibrosis.20 Also, in these patients, treatment duration cannot be reduced indiscriminately without compromising efficacy. All existing trials reserved a short (<16 weeks) treatment duration only to patients with wk4-R. Indeed, in the ACCELERATE study, patients were randomised to short or standard treatment duration independently of the week4-R: overall, relapse rates were more frequently observed in patients treated with a short treatment than in those treated until week 48 (51% vs 18%). However, in a secondary analysis, the rate decreased to 14% in patients with wk4-R,25 in accordance with values of 10–12% reported in other trials (table 2).20–24 In an effort to further reduce this rate, we have explored other determinants of relapse; in patients with wk4-R, the relapse rate after 12 weeks was higher among those with platelet count <140 000 mm$^3$ and BMI <30 kg/m$^2$; lean patients with normal platelet counts and wk4-R had only an 8.2% likelihood of relapse after short treatment.27

EXTENDED TREATMENT DURATION FOR PATIENTS WITHOUT WEEK 4 VIRAL CLEARANCE

Treatment extension is a new concept in HCV therapy. In a retrospective analysis of genotype 1 patients treated with Peg-IFNα-2b and ribavirin, Drusano and Preston have suggested that the duration of therapy after the first undetectable HCV-RNA was important in maximising the likelihood of SVR; because the average time to clear HCV-RNA was over 30 weeks, treatment as long as 52–56 weeks after the first undetectable HCV-RNA was estimated to maximise SVR.30 Following this indication, the recommended 48 week treatment appears inadequate for most patients with genotype 1, given that, in late responders, treatment would not be long enough to allow viral clearance from all body reservoirs.

Genotype 1

Initial evidence supporting the benefit of treatment beyond 48 weeks has been provided by Buti et al.28 In this proof-of-concept report, nine patients with >2 log HCV-RNA decline at week 12 and undetectable HCV-RNA at week 24 were kept on treatment until week 72: by extending the treatment, SVR was attained in 77% of patients.29 The first randomised study that tested the hypothesis of a better outcome after an extended treatment duration was published by Berg et al.30 In this German study all patients were randomised at baseline to Peg-IFNα-2a and ribavirin (800 mg/day) to 48 or 72 week duration: the observed SVR rates were 53% and 54%, data that disclaimed the experimental hypothesis. However, at a post hoc analysis the subset of patients who were HCV-RNA positive at week 4 achieved higher SVR when treated for 72 weeks rather than for 48 weeks (29% vs 17%).30 A more appropriate design was adopted in a Spanish trial where only patients still viraemic at week 4 were randomised to 48 or 72 week therapy with Peg-IFNα-2a and ribavirin (800 mg/day). End-of-treatment virological responses were similar in the two arms, but SVR rates were higher in the extended treatment arm (45% vs 32%).31 It should be noted that suboptimal doses of ribavirin used in the above-mentioned trials might have impacted negatively on the overall results. A study in the United States randomised patients with >2 log drop at week 12 but with undetectable HCV-RNA at week 24 to complete 48 or 72 weeks of therapy with Peg-IFNα-2b and an appropriate dose (800–1400 mg/day) of ribavirin. End-of-treatment virological response was similar between the two treatment arms (45% vs 48%). However, the relapse was lower in the extended treatment group (19% vs 33%), and the benefit was offset by a higher dropout rate (15% vs 7%). When only patients who completed treatment were evaluated, treatment for 72 weeks increased SVR rates (38% vs 18%).32 The same subgroup of genotype 1 patients and slow response, ie, those who were still viraemic at week 12 but with undetectable viraemia at week 24, were randomised to either 48 or 72 weeks of Peg-IFNα-2b and ribavirin (800–1400 mg/day) in the

Table 1

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Treatment duration (weeks)</th>
<th>Total number of patients</th>
<th>Cut-off for low viraemia (IU/ml)</th>
<th>Patients with RVR (number, %)</th>
<th>EOT in RVR patients %</th>
<th>Relapse rate in RVR patients %</th>
<th>SVR in patients with RVR (number, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeuzem25</td>
<td>Cohort†</td>
<td>24</td>
<td>235</td>
<td>600 000</td>
<td>110 (47)</td>
<td>97</td>
<td>8</td>
<td>98 (88)</td>
</tr>
<tr>
<td>Jensen‡</td>
<td>Post-hoc analysis*</td>
<td>48</td>
<td>118</td>
<td>–</td>
<td>33 (28)</td>
<td>97</td>
<td>9</td>
<td>29 (88)</td>
</tr>
<tr>
<td>Yu23</td>
<td>RCT†</td>
<td>48</td>
<td>271</td>
<td>–</td>
<td>55 (20)</td>
<td>53</td>
<td>3</td>
<td>50 (81)</td>
</tr>
<tr>
<td>Lui17</td>
<td>RCT‡</td>
<td>24</td>
<td>100</td>
<td>400 000</td>
<td>45 (45)</td>
<td>100</td>
<td>11</td>
<td>58 (56)</td>
</tr>
<tr>
<td>Mangia16</td>
<td>Prospective</td>
<td>24</td>
<td>154</td>
<td>800 000</td>
<td>104 (65)</td>
<td>91</td>
<td>17</td>
<td>73 (76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48</td>
<td>154</td>
<td>800 000</td>
<td>97 (63)</td>
<td>97</td>
<td>2</td>
<td>94 (77)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
<td>459</td>
<td>–</td>
<td>123 (27)</td>
<td>95</td>
<td>18</td>
<td>62 (26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48</td>
<td>237</td>
<td>–</td>
<td>62 (26)</td>
<td>97</td>
<td>10</td>
<td>54 (87)</td>
</tr>
</tbody>
</table>

Italic type indicates the post hoc analysis of the trial by Yu23 made according to viremia levels of 400,000.

*In the subset of patients treated with weight-based ribavirin dosing.

†Secondary analysis.

‡Post hoc analysis.

EOT, end of therapy; RCT, randomised controlled trial; RVR, rapid virological response; SVR, sustained virological response.
trial by Buti and colleagues: in an intent-to-treat analysis, SVR rates were 43% and 48%, respectively. Nevertheless, patients who were 80/80/80 compliant had SVR rates of 44% and 57% after 48 or 72 weeks of therapy.33

It seems likely that genotype 1 patients with a wk12-R could be dichotomised even further, into those who attain undetectable serum HCV-RNA at week 8 (wk8-R) versus those with wk12-R, and that these two subgroups might benefit from different durations of treatment. We tested this hypothesis in a randomised clinical trial where patients with wk8-R were allocated to 48 weeks of treatment and achieved a 70% SVR rate, whereas those with wk24-R were randomised to 48 or 72 weeks duration: SVR rates were 63% in the extended arm and 38% in the standard arm.13 This study has clearly established the value of evaluating viral clearance at treatment week 8, and has outlined the need for treatment extension in patients who first attain undetectable HCV-RNA at week 12.

How long treatment should last in slow responders remains unanswered on a rational basis. Ide and co-workers from Japan evaluated serum HCV-RNA monthly, up to week 24 from the start of Peg-IFNα-2b and ribavirin, and administered 44 more weeks of therapy once the levels became first undetectable: ie, for a patient with wk8-R, total length of treatment lasted 52 weeks, while for a patient with wk24-R therapy was given until week 68.34 This study confirmed the usefulness of a monthly evaluation of serum HCV-RNA, and further showed that patients with wk8-R could achieve a 90% SVR rate after a total treatment length of 52 weeks. More impressive results were registered in patients with week 16–24 response who cleared the infection in 9% of cases (1/11) after 48 weeks of therapy, and in 78% (7/9) when treatment was extended up to 60–68 weeks. The idea beyond this innovative schedule warrants further investigation in trials with adequate sample size.

Additional evidence on the need to treat for longer than 48 weeks patients who become HCV-RNA negative at week 12 has recently been reported, though indirectly, by Berg and colleagues in their recently published study.19

**Genotypes 2 and 3**

The optimal duration of treatment in patients with genotypes 2 and 3 without wk4-R remains undetermined. In these patients disappointing SVR rates were reported either after short or standard 24 week duration: 26% versus 45% in the study by Shiffman et al,25 and 41% versus 62% in the study by Lagging.35 Thus, the issue of increasing length of treatment for patients infected with genotypes 2 or 3, without wk4-R, needs future exploration. Preliminary evidence exists to support longer treatment for this subset of patients. As shown in a retrospective analysis of data from two randomised, phase III studies in which patients were treated with Peg-IFNα-2a and ribavirin at a dose of 1000–1200 mg daily, prolonging treatment to 48 weeks yielded similar rates than therapy administered for 24 weeks: 67% versus 65%.36 37

### CONCLUSIONS

Individualised treatment appears the best strategy for a rational use of resources and distinctive algorithms for treating HCV-infected patients are given in figs 1 and 2. Either for patients with easy-to-cure genotype and for those with difficult-to-cure genotypes, antiviral therapy needs to be individualised according to the first on-treatment HCV-RNA undetectability. Regardless of genotype, evidence has accumulated to support the week 4 response (wk4-R) as the strongest predictor of SVR in clinical practice and the criterion to be used to reduce duration of treatment. In order to ensure the highest likelihood of success after short treatment and to prevent relapse, two notes of caution should be considered: at variance with the indicated dosages, ribavirin needs to be administered on a weight-based dosage. Moreover, a wk4-R should not be taken as the only rule to tailor length of treatment, as normal body

### Table 2

<table>
<thead>
<tr>
<th>Reference</th>
<th>SVR after 12–16 weeks (%)</th>
<th>Relapse rate (%)</th>
<th>SVR after 24 weeks (%)</th>
<th>Relapse rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mangia21</td>
<td>85</td>
<td>10</td>
<td>91</td>
<td>2</td>
</tr>
<tr>
<td>Yu24</td>
<td>94</td>
<td>6</td>
<td>95</td>
<td>3</td>
</tr>
<tr>
<td>Dalgard23</td>
<td>81</td>
<td>14</td>
<td>91</td>
<td>7</td>
</tr>
<tr>
<td>Shiffman25</td>
<td>79</td>
<td>14</td>
<td>85</td>
<td>7</td>
</tr>
</tbody>
</table>

SVR, sustained virological response.
weight and lack of advanced liver damage for patients with genotypes 2 and 3, and low viremia levels for patients with genotype 1 may assist to better refine candidates for short therapy.

Should 72 weeks of Peg-IFN and ribavirin be recommended for patients who have a slow HCV RNA clearance? It is unclear which definition of non-responders should be used to select patients for 72 weeks of treatment. Our suggestion would be to adopt the timing of the first undetectable HCV-RNA on treatment, and to leave aside the criterion of a 2 log decline in viremia from baseline. Several prospective studies confirmed that patients who first achieve undetectable HCV-RNA at week 24 have decreased relapse rates and improved SVR when treated with extended duration of therapy. Two prospective studies indicated that patients with genotype 1 with wk8-R benefit from 48 weeks of treatment. Data on the use of wk12-R are more heterogeneous, with two prospective studies suggesting benefits from 72 weeks of therapy. Many question are still unanswered, the main one being whether treatment should be extended for patients with genotypes 2 and 3 without RVR and how long.

Even if prolonging treatment to subgroups should yield better results, it needs to be determined whether prolongation (from 12 to 24 weeks, from 48 to 72 weeks) is cost effective. Such analysis is mostly absent and this makes it difficult to draw clear recommendations concerning guided treatment.

### REFERENCES


Editor’s quiz: GI snapshot

Emad El-Omar, editor

Transfusion-refractory anaemia in liver cirrhosis

CLINICAL PRESENTATION

A 33-year-old man with chronic alcoholism presented with anaemia. Investigations showed haemoglobin 7.5 g/dl (reticulocytes: 11.2%), leucocytes 4.7 × 10^9/l, platelets 61 × 10^9/l, direct bilirubin 221 (reference <6) μmol/l, aspartate transaminase 109 (reference 15–38) U/l, alanine transaminase 38 (reference 8–58) U/l, γ-glutamyltransferase 31 (reference 11–62) U/l, lactate dehydrogenase 319 (reference 118–221) U/l, haptoglobin <0.06 (reference 0.16–1.97) g/l, methaemalbumin 0.18 (reference <0.1) mg/dl and a negative direct antiglobulin test. The iron status, cholesterol and triglyceride profiles were unremarkable. On referral, physical examination showed pallor, jaundice, hepatomegaly (3 cm), splenomegaly (10 cm) and ascites. Seven units of blood were transfused without improvement of his anaemia. Trans-jugular liver biopsy confirmed alcoholic cirrhosis. The peripheral blood film showed dysmorphic red cells (fig 1A, arrows).

QUESTION

What was the diagnosis?

See page 114 for answers