Treatment of Chronic Hepatitis C in Naive Patients

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Treatment of naive patients with chronic hepatitis C has already been reviewed in international consensus meetings [1, 2]. The first consensus was held in Paris and standard interferon in combination with ribavirin was judged to be the best treatment for naive patients [1]. Later in 2002 the National Institutes of Health (NIH) consensus meeting stated that pegylated interferon in combination with ribavirin was the optimal treatment for chronic hepatitis C [2, 3]. There is no doubt that pegylated interferon is better than standard interferon and results in higher response rates, is easier to administer, and generally allows a better quality of life for patients during treatment, both as monotherapy and in combination with ribavirin [4-9]. Thus, at present the gold standard for treatment of naive patients with chronic hepatitis C is pegylated interferon in combination with ribavirin [2].

TREATMENT WITH THE COMBINATION OF PEGYLATED INTERFERON WITH RIBAVIRIN

The pivotal trials evaluating pegylated interferons have used either pegylated interferon-alpha-2b or -2a, different doses of pegylated interferon and ribavirin [6-8]. In the study by Manns et al. pegylated interferon-alpha-2b with a low 0.5µg/kg body weight once weekly (BW QW) (after a 4 weeks induction period with high dose) in combination with ribavirin 1000/1200mg q.d. or a high dose pegylated interferon-alpha-2b (1.5µg/kg BW QW) in combination with a fixed
800mg dose of ribavirin was compared with standard combination therapy (interferon-alpha-2b 3MU t.i.w. plus ribavirin 1000/1200mg depending on weight) [6]. The 1.5µg pegylated interferon-alpha-2b dose arm resulted in the highest overall sustained virologic response (SVR) rate (Figure 1). In the study by Fried et al., pegylated interferon-alpha-2a with a fixed dose (180µg QW) in combination with ribavirin 1000 or 1200mg depending on weight was compared with pegylated interferon-alpha-2a monotherapy, and standard combination therapy [7]. The overall SVR rate was highest in the pegylated interferon plus ribavirin arm (Figure 2). Treatment lasted 48 weeks for all patients in these studies, and a 24 week treatment schedule, which had been recommended for genotypes 2 and 3 at the Paris consensus meeting with standard combination therapy, was not evaluated. The length of treatment (24 versus 48 weeks) and ribavirin dose (800mg vs. 1000-1200mg) was further evaluated in a 4-armed study with pegylated interferon-alpha-2a with a fixed dose (180µg QW). In this study randomized patients were stratified according to genotype and viral load, with a pre-planned unequal distribution of difficult-to-treat patients (genotype 1 and or a high viral load) to the longer treatment making the overall results not applicable for comparison with other studies, but allowing assessment of response by genotype and viral load [8]. This study confirmed that a 24 week treatment was sufficient for genotypes 2 and 3 whereas 48 weeks was needed for genotype 1. A 24-week treatment schedule for genotype 2 or 3 has also recently been evaluated for pegylated interferon-alpha-2b (dosed 1.5µg/kg BW QW) in combination with ribavirin (800–1400mg q.d. depending on BW), and has been found to provide the same results as a 48-week schedule in the registration study [10]. No head to head comparison of the two approved pegylated interferons has been conducted but the above mentioned studies indicate that both pegylated interferons when combined with ribavirin are better than standard combination therapy.
Figure 1: Sustained virologic response (SVR) (%) in registration study on pegylated interferon-alpha-2b by Manns et al. [6] according to treatment arm.

Figure 2: Sustained virologic response (SVR) (%) in registration study on pegylated interferon-alpha-2a by Fried et al. [7] according to treatment arm.
In these previous pivotal studies genotype was the strongest baseline factor to predict a sustained virologic response followed by viral load, extent of fibrosis, race, weight, alanine aminotransferase (ALT) quotient and gender. Furthermore, sustained virologic response has been the primary end-point in these studies and is the best indicator of a favorable response as well as an indication of eradication and cure for most patients during long-term follow-up [11]. Hence, this paper will review SVR separately according to genotype based primarily on these pivotal trials.

TREATMENT OF CHRONIC HEPATITIS C CAUSED BY GENOTYPE 2 OR 3

In the 2 pivotal registration studies [6, 7] only 48-week schedules were used, and not a 24-week schedule which had been judged to be sufficient for genotypes 2 and 3 with standard combination therapy [1]. However, a 24 week combination treatment with pegylated interferon-alpha-2a 180µg QW in combination with ribavirin 800mg or weight based 1000-1200mg q.d. was shown to result in the same SVR as the 48 week treatment schedule, 81-84% versus 79-80%, respectively, in patients with genotype 2 or 3 [8]. The same findings were found for pegylated interferon-alpha-2b when dosed 1.5µg/kg BW and given in combination with ribavirin dosed 800-1400mg q.d. according to weight [10]. This latter study only included a 24 week treatment arm but the overall 81% SVR rate was comparable to the 82% reached in the 48-week treatment arm in the registration study [6]. Thus, the optimal treatment length for genotypes 2 and 3 is 24 weeks and not 48 weeks since the shorter treatment reaches the same SVR rate as the longer, and is more cost-effective. Although treatment periods of less than 24 weeks seem to be sufficient in a subset of patients with genotype 2 or 3, for the moment, this has only been evaluated in small studies reported in abstract form.

On the other hand, certain monotherapy studies have indicated that lower pegylated interferon doses might be sufficient for genotypes 2 and 3 since 1.0µg/kg BW of pegylated interferon-alpha-2b and 135µg of interferon-alpha–2a have resulted in SVR rates that are similar or better than higher doses [4, 12]. However, lower doses of pegylated interferon in combination with ribavirin have only been investigated in small uncontrolled studies which have showed similar
results to those in randomized controlled studies with higher doses [13].

The SVR for genotype 2 and 3 with pegylated interferon-alpha-2a 180µg plus ribavirin are given according to ribavirin dose and viral load (low ≤800,000IU/mL versus high >800,000IU/mL) in Table 1a [8], and with pegylated interferon-alpha-2b 1.5µg/kg BW plus ribavirin 800-1400mg depending on BW according to viral load (low ≤600,000IU/mL versus high >600,000IU/mL) in Table 1b [10]. Results in patients with genotype 2 or 3 are also given separately in Table 1b.
**Table 1:** SVR at follow-up 24 weeks after treatment has been discontinued in patients with chronic hepatitis C caused by genotype 2 and 3 with pegylated interferon-alpha-2a (Table 1a) and pegylated interferon-alpha-2b (Table 1b) according to viral load.

<table>
<thead>
<tr>
<th>Ribavirin dose</th>
<th>Treatment length</th>
<th>All</th>
<th>LVL</th>
<th>HVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>800mg</td>
<td>24 weeks</td>
<td>84%</td>
<td>85%</td>
<td>84%</td>
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<tr>
<td>1000/1200mg</td>
<td>24 weeks</td>
<td>81%</td>
<td>83%</td>
<td>80%</td>
</tr>
<tr>
<td>800mg</td>
<td>48 weeks</td>
<td>79%</td>
<td>88%</td>
<td>74%</td>
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<tr>
<td>1000/1200mg</td>
<td>48 weeks</td>
<td>80%</td>
<td>77%</td>
<td>82%</td>
</tr>
</tbody>
</table>

**Table 1a:** SVR (%) in patients with genotype 2 and 3 treated with pegylated interferon-alpha-2a 180µg according to ribavirin dose, treatment length, and viral load (low ≤800,000IU/mL (LVL) versus high >800,000IU/mL (HVL), Cobas Amplicor HCV Monitor Test, version 2.0, Roche Diagnostics, Branchnburg, New Jersey) [8].

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment length</th>
<th>All</th>
<th>LVL</th>
<th>HVL</th>
</tr>
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<tr>
<td>2 and 3</td>
<td>24 weeks</td>
<td>81%</td>
<td>87%</td>
<td>74%</td>
</tr>
<tr>
<td>2</td>
<td>24 weeks</td>
<td>93%</td>
<td>95%</td>
<td>91%</td>
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<tr>
<td>3</td>
<td>24 weeks</td>
<td>79%</td>
<td>86%</td>
<td>70%</td>
</tr>
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</table>

**Table 1b:** SVR (%) in patients with genotype 2 or 3 treated with pegylated interferon-alpha-2b 1.5µg/kg BW plus ribavirin 800-1400mg depending on body weight according to viral load (low ≤600,000IU/mL (LVL) versus high >600,000IU/mL (HVL), real time polymerase chain reaction technology, lower limit of detection 29IU/mL) [10].
The overall SVR results in these studies are very similar, 84 and 81%, respectively. Results from the Hadziyannis study clearly indicate that 24 weeks of treatment with a fixed pegylated interferon-alpha-2a dose of 180µg QW is sufficient when combined with a 800mg ribavirin dose (low compared to the 1000/1200mg standard dose). This indicates that the dose of ribavirin can be lower in genotype 2 and 3 infections than in genotype 1. The SVR rate was the same in patients with high and low viral load in this study when genotypes 2 and 3 were analysed together. In the study by Zeuzem et al. both pegylated interferon-alpha-2b and ribavirin were dosed according to body weight. The overall SVR was in the same range as with pegylated interferon-alpha-2a plus ribavirin in the Hadziyannis study when genotype 2 and 3 were combined, but patients with high viral loads (>600,000IU/mL) responded less well and had an SVR of 74%. When the SVR was analysed separately for genotypes 2 and 3, a lower SVR was found but only in patients with genotype 3 who had high viral loads (Table 1b). The SVR rates in genotype 3 patients with high viral baseline loads was not published separately in the pegylated interferon-alpha-2a study by Hadziyannis et al. so no data are available. In the pegylated interferon-alpha-2b study by Zeuzem et al. the lower SVR rate in genotype 3 patients with high viral loads mainly seemed to be caused by a higher relapse rate in this category (23%) compared to patients with genotype 2 with low or high viral loads and genotype 3 with low viral loads (5-9%) [10]. These two studies indicate that different doses of ribavirin, a lower 800mg fixed dose versus a higher weight-based dose (800-1400mg) respectively are optimal when combined with pegylated interferon-alpha-2a and -2b respectively. The optimal dosing of ribavirin, however, has not yet been fully clarified, and results from population pharmacokinetic analysis suggest that it may be better to dose ribavirin according to renal function and not to body weight alone [14].

TREATMENT OF CHRONIC HEPATITIS C CAUSED BY GENOTYPE 1

The likelihood of achieving an SVR is predicted by pre-treatment patient characteristics, as well as the early virologic response. The strongest predictor for response is genotype. For the more difficult to treat genotype 1 infections, a 48 week treatment schedule is necessary, and improves results obtained with shorter treatment schedules [8].
The results obtained in three pivotal pegylated interferon plus ribavirin studies [6-8] are shown in Table 2.

In the registration pegylated interferon-alpha-2a study, a fixed 180µg interferon dose was used in combination with a 1000-1200mg weight-based ribavirin dose, a treatment schedule which also provided the highest SVR rate in the 4-armed study evaluating ribavirin dose (800mg versus 1000/1200mg) and treatment length (24 versus 48 weeks) [7, 8]. The overall SVR with pegylated interferon-alpha-2a 180µg plus the weight-based ribavirin dose in these studies was 46-52% (Table 2a). The corresponding SVR rates in patients with low or high baseline viral loads were 56-65% versus 41-47%, respectively.

Table 2: SVR at follow-up 24 weeks after treatment has been discontinued in patients with chronic hepatitis C caused by genotype 1 with pegylated interferon-alpha-2a (Table 2a) and pegylated interferon-alpha-2b (Table 2b) according to viral load and ribavirin dose.

<table>
<thead>
<tr>
<th>Ribavirin dose</th>
<th>Treatment length</th>
<th>All</th>
<th>LVL</th>
<th>HVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000/1200mg</td>
<td>48 weeks</td>
<td>46%</td>
<td>56%</td>
<td>41%</td>
</tr>
<tr>
<td>800mg</td>
<td>48 weeks</td>
<td>41%</td>
<td>55%</td>
<td>36%</td>
</tr>
<tr>
<td>1000/1200mg</td>
<td>48 weeks</td>
<td>52%</td>
<td>65%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Table 2a: SVR (%) in patients with genotype 1 treated with pegylated interferon-alpha-2a 180µg according to ribavirin dose, and viral load (low ≤800,000IU/mL (LVL) versus high >800,000IU/mL (HVL), Cobas Amplicor HCV Monitor Test, version 2.0, Roche Diagnostics, Branchburg, New Jersey) [7, 8].
Treatment of Naive Patients

<table>
<thead>
<tr>
<th>Ribavirin dose</th>
<th>Treatment length</th>
<th>All</th>
<th>LVL</th>
<th>HVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>800mg</td>
<td>48 weeks</td>
<td>42%</td>
<td>73%</td>
<td>30%</td>
</tr>
<tr>
<td>≤10.6mg/kg BW</td>
<td>48 weeks</td>
<td>38%</td>
<td>74%</td>
<td>27%</td>
</tr>
<tr>
<td>&gt;10.6mg/kg BW</td>
<td>48 weeks</td>
<td>48%</td>
<td>71%</td>
<td>37%</td>
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</tbody>
</table>

Table 2b: SVR (%) in patients with genotype 1 treated with pegylated interferon-alpha-2b 1.5µg/kg BW and ribavirin 800mg q.d. (with a post hoc calculation of ribavirin dose ≤10.6mg versus >10.6mg per BW) according to viral load (low ≤2,000,000 copies/mL corresponding to ≤800,000IU/mL (LVL) versus high >2,000,000 copies/mL corresponding to >800,000IU/mL (HVL), quantitative PCR assay National Genetics Institute, Los Angeles, CA, USA, lower limit of detection 100 copies/mL) [6].

In the registration pegylated interferon-alpha-2b study, the best results were obtained in the arm using a fixed 800mg dose of ribavirin in combination with a 1.5µg pegylated interferon-alpha-2b dose/kg BW [6]. An overall SVR of 42% was reached, and the highest SVR (73%) was found in patients with low baseline viral loads and the lowest SVR in patients with high baseline viral loads (30%) (Table 2b). The low ribavirin dose was selected because of concern that a higher dose of pegylated interferon-alpha-2b might be associated with anemia that would exacerbate that caused by ribavirin. A post hoc evaluation showed that patients who received a ribavirin dose of >10.6mg/kg BW had a better response than those receiving less than 10.6mg/kg. Nevertheless, only 37% of patients with genotype 1 and high viral loads reached SVR in the high ribavirin dose group (http://www.emea.eu.int/index/indexh1.htm), and only 27% of those in the low ribavirin dose group [6].

In these randomized, controlled studies the SVR was lower in patients with high baseline viral loads, who were older, heavier, and had bridging fibrosis or cirrhosis.
TREATMENT OF CHRONIC HEPATITIS C CAUSED BY GENOTYPE 4

Genotype 4 seems to be more difficult to treat than genotypes 2 or 3. A combined analysis of data from patients infected with HCV genotype 4 who were enrolled in the Hadziyannis and Fried pivotal studies revealed that SVR was obtained in 17/24 (79%) of the patients treated with pegylated interferon-alpha-2a 180µg QW plus ribavirin 1000/1200mg QD for 48 weeks [7, 8]. In contrast, none of the 5 patients treated with a lower dose of ribavirin for 24 weeks obtained an SVR [15]. This suggests that if genotype 4 is treated in the same way as genotype 1 with high dose ribavirin for 48 weeks results can be obtained that are similar to those with HCV genotype 2 or 3 infections.

EARLY VIROLOGIC RESPONSE (EVR)

The predictability of an SVR based on EVR has been assessed in studies with both pegylated interferon-alpha-2a and-2b [7, 16]. An EVR, defined as a decline of HCV RNA levels by at least 2 logs at week 12 of treatment, is a good indication that an SVR will occur. Conversely, and perhaps more important, in those without an EVR, 97 to 100% will not have an SVR. Thus lack of an EVR at week 12 is used as a criteria to stop treatment of pegylated interferon plus ribavirin.

COMPLIANCE TO TREATMENT

Treatment compliance is of major importance for the outcome [17]. There is a higher rate of SVR in patients who take 80% of the pegylated interferon dose and 80% of the ribavirin dose for 80% of the scheduled treatment period than in patients who do not. Compliance to treatment period is particularly important. This is especially true in patients with HCV genotype 1 and in patient populations with low virologic response. It is therefore extremely important to treat side-effects promptly and effectively to avoid unnecessary discontinuation of therapy [18]. Hence, 80/80/80 compliance increased SVR in genotype 1 infections from an overall 42% with pegylated interferon-alpha-2b/ribavirin to 63% [6, 17].
ADVERSE EVENTS

In general, the incidence and types of side-effects with pegylated interferons combined with ribavirin are similar to those for standard interferon plus ribavirin.

Adverse events associated with pegylated interferon-alpha are bone marrow suppression with neutropenia and thrombocytopenia which seem to be somewhat more pronounced with pegylated interferon than standard interferon. The initial flu-like symptoms and decline in health related quality of life during treatment seem to be less pronounced with pegylated interferons than with standard interferons [9, 18].

Side-effects typically associated with ribavirin are hemolytic anemia, fatigue, itching and rash. Ribavarin-induced reactions depend primarily on serum concentrations of ribavirin, and not on the dose per kg BW [19].

CONCLUSIONS

Treatment for both HCV genotype 1 and probably genotype 4 with pegylated interferon-alpha plus ribavirin should be for 48 weeks, with a standard ribavirin dose (1000mg for patients weighing ≤75 kg and >1200mg for those >75kg). Either pegylated interferon-alpha-2a 180µg or pegylated interferon-alpha-2b 1.5µg/kg body weight once a week can be used. Quantification of serum HCV RNA should be performed at baseline and at week 12 during therapy to evaluate if a reduction in HCV RNA levels of at least 2 logs has occurred corresponding to an early viral response. Treatment should be discontinued in patients with no EVR. For genotypes 2 and 3, pegylated interferon and ribavirin for 24 weeks is sufficient and the ribavirin dose can be reduced to 800mg if needed. Further studies should be performed to see if lower pegylated interferon doses and shorter treatment times can be used for genotype 2 and 3 infections.
REFERENCES


