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REVIEW

# Expert opinion on the treatment of patients with chronic hepatitis C

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SUMMARY. The current preferred treatment for patients with hepatitis C virus (HCV) is combination therapy consisting of pegylated interferon alfa and ribavirin (RBV) for 24–48 weeks. Although this approach appears to be highly effective for patients with HCV genotypes 2 or 3, who have a sustained virological response (SVR) of approximately 80%, the treatment algorithm is less effective for patients with HCV genotype 1, as these patients have SVR rates of just 40–50%. In order to improve treatment outcomes, this article explores potential approaches for the optimization of treatment for patients with HCV genotype 1: considering shorter treatment periods for patients with a rapid virological response (RVR), increasing treatment periods for slow responders, and increasing RBV dose are all suggestions. Results from clinical trials suggest that approximately 20% of the HCV genotype 1-infected population are slow responders, and around 15% of all HCV genotype-1 infected patients could benefit from a shorter treatment duration without compromising the SVR rate. Interest has also focused on whether treatment duration could be individualized in some patients with genotype 2 and 3 infection. Here all the findings from recent studies are translated into practical advice, to help practitioners make evidence-based treatment decisions in everyday clinical practice. Although there are areas where currently available data do not provide conclusive evidence to suggest amending treatment approaches, there is clearly potential for individualized treatment in all aspects of hepatitis treatment in the future.

*Keywords*: hepatitis C, pegylated interferon alfa, ribavirin, treatment, virological response.

## INTRODUCTION

Current treatment algorithms result in rates of sustained virological response (SVR) of ~80% in patients infected with HCV genotypes 2 or 3, suggesting that some of the primary challenges in the management of chronic hepatitis C (CHC) have now been resolved. However, in patients infected with HCV genotype 1, the standard combination treatment of 48 weeks of pegylated interferon alfa (peginterferon) and ribavirin (RBV) results in SVR rates of only 40–50% [1,2], with higher rates following 48 weeks rather than with 24 weeks of treatment (51% *vs* 41%, respectively) [3]. Emerging data suggest that treatment duration may be shortened or lengthened depending on baseline viral load and virological response at week 4 and/or week 12. This paper considers these results and their implications for treatment optimization and suggests how this latest research can be translated into everyday clinical practice.

Abbreviations: ALT, alanine-aminotransferase; cEVR, complete early virologic response; CHC, chronic hepatitis C; EOT, end-of-treatment; HCV, hepatitis C virus; LVL, low-viral load; pEVR, partial early virologic response; RBV, ribavirin; RVR, rapid virological response; SVR, sustained virological response.

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## ISSUES UNDER CONSIDERATION

Principal considerations for treatment of CHC include dose and duration of antiviral therapy (along with related costs), quantification of baseline HCV RNA levels, the definition of response during the early stages and at the end of treatment, as well as the duration of the post-treatment follow-up

period. In addition, there remain a number of areas of uncertainty that have also to be taken into consideration, such as the variation in baseline viral load, monitoring time points and the 'time window' within which monitoring needs to take place.

### *Current treatment algorithm for treatment of patients with HCV*

Current treatment recommendations for patients chronically infected with HCV are shown in Fig. 1 [4–6]. Briefly, patients with genotype 2 or 3 infection are more responsive to the current standard of care of peginterferon plus RBV than those with genotype 1 or genotype 4 infection. The rates of SVR for genotype 2 or 3 infection are similar in patients treated for 24 or 48 weeks; thus, for these patients 24-week treatment is generally considered appropriate. For patients infected with HCV genotype 1, the recommended treatment duration is 48 weeks of peginterferon with RBV. While standard doses for peginterferon alfa-2a (180 $\mu$g, qw) and peginterferon alfa-2b (1.5 $\mu$g/kg, qw) are well established, different recommendations exist for RBV dose according to HCV genotype and type of peginterferon [7,8]. It appears that lower doses of RBV are required for treatment of patients infected with HCV genotype 2 or 3 than for genotypes 1 or 4 [9,10]. For the standard duration of treatment of HCV genotype 1 and 4 infection, weight-based RBV doses of 800–1200 mg, qd, or up to 1400 mg for patients above 105 kg, are recommended, while no additional benefit of RBV doses higher than 800 mg in HCV genotype 2 and 3 infection was observed in several studies [3,11]. Available data for patients infected with genotype 5 or 6 are limited; therefore, combination treatment with 1000/1200 mg, qd, RBV for 48 weeks is currently recommended.

### *Determination and monitoring of viral load*

The decision on whether to continue or stop therapy should primarily be based on the level of HCV RNA during treatment. Therefore, it is necessary to measure viral load accurately. Important aspects to consider in this respect are the natural fluctuations in viral load during infection, as well as intra-assay (within an individual test) and inter-assay (between different tests) variability. Currently available commercial assays vary considerably in their dynamic ranges of quantification (Table 1). Despite the introduction of international units per mL (IU/mL) for reporting viral load, discrepancies may occur when patients are monitored using different types of assay [14–19]. For example, rules for early discontinuation at week 12 and 24, as well as rules for determination of treatment duration [baseline viral load, RVR, complete early viral response (cEVR)], were established mainly with standard RT-PCR based assays, which have since been replaced by real-time PCR-based assays with higher sensitivity and broader dynamic range of linear HCV RNA quantification. The differences between commercial HCV RNA assays have been well documented in several studies [15–19], with the majority of studies showing an intra-assay variability of approx. 0.2 log. Generally, comparisons between Amplicor Monitor and CAP/CTM yielded comparable results (±0.2 log), whereas comparisons between bDNA and Abbott real-time HCV on the one hand and CAP/CTM on the other showed a difference of 0.5–0.7 log. Additionally, HCV RNA viral load decline assessed during antiviral therapy can give different results, regardless of the use of IUs. False-positive and false-negative results, as well as variations in the HCV RNA level of up to 2 $\log_{10}$ IU, have been observed, which may well have an impact on the management of patients, particularly if treatment decisions are made using a single HCV RNA assessment [15,16,19].

**Genotype 1 (and 4, 5 or 6)**

- Determine baseline viral load
- Initiate 48 week course of treatment with peginterferon and RBV (weight-based qd)
- Determine early virological response (EVR) at week 12

  If viral load dropped by ≥2 log (i.e. 100-fold) from baseline, continue treatment for a total of 48 weeks, provided HCV RNA is undetectable at week 24, using a sensitive test (limit of detection ≤50 IU/mL)

  If viral load dropped by <2 log change treatment strategy: stop treatment

**Genotype 2 and 3**

- Initiate 24 week course of treatment with peginterferon and RBV (800mg qd)

  There is no recommendation to measure HCV RNA at week 12 in genotype 2 and 3 infection, given the high response rate

**Fig. 1** Overview of current treatment guidelines (based on references [4–6,12,13]).

**Table 1** Detection limits and range of linear quantification for HCV RNA tests [20]

| Test | Detection limit (cut-off) IU/mL | Dynamic range of linear quantification IU/mL | |
|---|---|---|---|
| | | Lower limit | Upper limit |
| Qualitative assays | | | |
| Versant qualitative assay (Siemens, Eschborn, Germany) | 5–10 | NA | NA |
| Cobas Amplicor v2.0 (Roche, Mannheim, Germany) | 50 | NA | NA |
| Quantitative assays | | | |
| Abbott Real Time | 10 | 12 | 100 000 000 |
| Cobas TaqMan real-time PCR assay (Roche) | 10 | 43 | 69 000 000 |
| Cobas Amplicor Monitor v2.0 (Roche) | 600 | 600 | 500 000 |
| Versant HCV RNA 3.0 (Bayer) | 615 | 615 | 7700 000 |

Practitioners should be careful not to attach undue clinical significance to small changes (<0.5 $\log_{10}$) in serum HCV RNA level. The clinical relevance of serial HCV viral level measurements in a patient is dependent on continuous use of the specific quantitative assay employed in the initial determination of the viral level. This may imply repeated testing in some cases; but these extra costs may be justified if they affect treatment management decisions.

## GENOTYPE 1

### *Week 12 stopping rule for patients with HCV genotype 1*

The current week 12 stopping rule recommends that patients without a ≥2 $\log_{10}$ drop in viral load compared to baseline (between 19% and 29% of patients with genotype 1 infection) discontinue therapy since the likelihood of achieving SVR with continued treatment is small; the negative predictive value is almost 100% [21,22]. Over-treatment of patients who have an extremely low chance of achieving SVR is thus avoided and valuable resources can be reserved for patients with a higher chance of treatment success [23]. Week 12 monitoring should be carried out as close as possible to the week 12 time point, ideally ±5 days, using a test with high sensitivity and wide dynamic range. Whether the 2 $\log_{10}$ drop represents the most accurate cut-off level for the decision on treatment termination or proceeding remains to be determined in prospective clinical studies. It is likely that with greater use of more sensitive assays with a broader range of linear quantification (e.g. real-time PCR assays), this parameter may be refined/adjusted in the near future. It may also be the case that new drugs currently in development will require different threshold levels and/or stopping rules based on their different modes of action, although this remains to be seen.

### *Assessment at week 24 in patients with HCV genotype 1*

If, at week 12, HCV RNA remains detectable but the viral load has dropped by at least 2 $\log_{10}$ (i.e. 100-fold) from baseline, treatment should be continued for the full 48-week course. However, if the patient remains HCV RNA positive at week 24, it is unlikely that an SVR will be achieved (negative predictive value 98–100%), [2,21,24], and, unless the patient is considered at high risk due to rapidly progressing fibrosis, treatment termination at week 24 can be considered. Studies are ongoing to determine whether patients may derive some benefit from treatment with peginterferon monotherapy, despite a lack of virological response. These include the COPILOT study comparing colchicine with low-dose peginterferon alfa-2b [25,26], which showed both high rates of premature discontinuation of therapy and that maintenance therapy with peginterferon was associated with improved disease free survival almost exclusively in patients with portal hypertension, and the EPIC3 program with peginterferon alfa-2b [27]. Recent results from the HALT-C trial [28], which investigated the effect of treating non-responders with peginterferon alfa-2a and RBV concluded overall that long-term therapy with peginterferon did not reduce the rate of disease progression and so do not support maintenance therapy in patients with HCV and advanced hepatic fibrosis who are prior non-responders. Interestingly, a significant decline in clinical outcomes was observed in patients with chronic HCV and advanced fibrosis or cirrhosis who achieved a profound decline in HCV RNA, defined as >4 log and/or undetectable with subsequent breakthrough or relapse, suggesting that a small subgroup of patients may benefit [29]. Unless results of the ongoing studies provide additional guidance, continued treatment of patients cannot be recommended.

### *Recommendations for optimizing treatment in patients with HCV genotype 1*

*Shorter treatment for patients with a rapid virological response*

The current 48-week treatment duration, recommended for HCV genotype 1-infected patients, may potentially result in the over-treatment of some genotype 1-infected patients who are more likely to achieve SVR, i.e. patients with low viral load before treatment and rapid virological response (RVR)

at week 4. Clearly it is desirable to expose patients to the shortest possible treatment duration – without compromising efficacy – in order to minimize the likelihood of adverse events and reduce costs. Hadziyannis *et al.* found that more than one third of individuals with HCV genotype 1 who were randomized to 24 weeks of therapy with pegylated IFNα-2a plus RBV achieved SVR [3]. Moreover, patients infected with HCV genotype 1 who became HCV RNA-negative by week 4, i.e. patients with RVR, were more likely to achieve SVR than those who did not become HCV RNA negative until week 12 [22]. A recent prospective trial demonstrated that patients with low baseline HCV RNA levels (≤600 000 IU/mL) and an RVR achieve an SVR rate of up to 90% (Fig. 2) [30]. Jensen *et al.* observed that almost a quarter (22.6%) of HCV genotype 1 patients treated with peginterferon plus RBV achieved RVR [31]. Of these patients, 89% showed SVR after treatment duration of only 24 weeks. Both pegylated interferons have recently been approved in the EU for shortened treatment duration of 24 weeks for HCV genotype 1 patients with low-viral load (LVL) (defined as <800 000 IU/mL for peginterferon alfa-2a and <600 000 IU/mL for peginterferon alfa-2b) and RVR [7,8]. To assure accurate determination of baseline viral load in cases with HCV RNA concentrations between 400 000 and 1 million IU/mL, physicians should consider performing two measurements using the same technique, from samples taken at least 4 weeks apart. Whether 10 or 50 IU is the most appropriate cut-off for determining RVR remains unclear, however, and is under investigation. Recently, Sarrazin *et al.* compared clinical outcomes for large cohorts of patients whose serum samples were analysed using both the COBAS TaqMan™ (detection limit approximately 10 IU/mL) and COBAS Amplicor™ (detection limit <50 IU/mL) assays. In this study, RVR rates and subsequent SVR rates were similar when RVR was defined as undetectable of below 15 IU/mL by the COBAS TaqMan assay in comparison with undetectable (<50 IU/mL) by the COBAS Amplicor assay, implying that HCV RNA levels rapidly decline not only to below 50 IU/mL but also below 15 IU/mL in patients achieving an RVR [15]. Interestingly, relapse rates were consistently lower in patients with undetectable HCV RNA at week 4 by COBAS TaqMan™ compared with COBAS Amplicor™, although the full significance of this remains to be established [15].

Patients should not be considered for shorter treatment duration if they have a baseline viral load above 600–800 000 IU/mL and/or have cirrhosis, are co-infected with HIV, or are immunosuppressed. Other factors influencing virological response that may also be considered include metabolic syndrome, insulin resistance and extensive steatosis. Zeuzem *et al.* demonstrated that the efficacy of peginterferon alfa-2a plus RBV is comparable between patients with genotype 1 infection and persistently normal alanine-aminotransferase (ALT) and those with elevated ALT levels [32]. However, SVR rates were significantly lower in those patients with persistently normal ALT treated for 24 weeks compared with 48 weeks (13% *vs* 40%, respectively), which also suggests that such patients may not be suitable candidates for shorter therapy. As this study of patients with persistently normal ALT did not include evaluation of RVR, it was not possible to identify a potential patient subgroup within this population (e.g. low viral load and/or RVR) who might benefit from shorter treatment.

## DETERMINING PRE-TREATMENT VIRAL LOADS AND DEFINING LOW *VS* HIGH-VIRAL LOADS

The definition and differentiation between low and high viral loads is still under discussion. Historically, pre-treatment

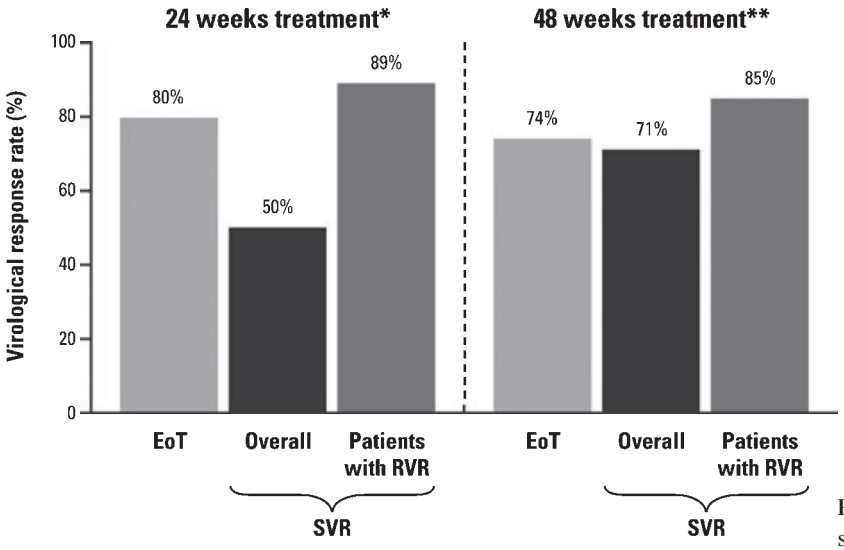


**Fig. 2** Rapid virological response predicts sustained virological response in HCV-1 infected patients with low baseline viral load (≤ 600 000 IU/mL).

viral load was classified as 'high' or 'low' using a cut-off of $2 \times 10^6$ copies/mL, based on data generated using conventional interferon-based regimens or pegylated interferon monotherapy [33,34]. When HCV RNA assays were standardized, conversion of copies/mL to IU/mL according to the WHO standard gave varying results depending on the assay used; 800 000 IU/mL has been recommended as the decision threshold for high versus low viraemia [35]. However, recent data suggest that a baseline level of 400 000 IU/mL is the most effective cut-off for a high or low probability to achieve SVR in genotype 1-infected patients [36,37]. This level was confirmed in a large 'real-life' experience study [38] and in a further study by Martinot-Peignoux and colleagues, with the caveat that it should be applied to treatment-naïve patients only [39]. In a recent study, pre-treatment HCV-RNA levels of 250 000 IU/mL best discriminated between genotype 1-infected patients with or without SVR after 24 weeks of therapy in patients with low pre-treatment viral load [37]. Whether a single cut-off level for pre-treatment viraemia is sufficient or whether several ranges of pre-treatment HCV RNA levels might allow for individualized treatment duration remains to be elucidated. Furthermore, cut-offs for low or high baseline HCV RNA concentration were established mainly on the basis of standard RT-PCR and bDNA assays and re-definition by the currently used real-time PCR-based assays is required. According to current data, treatment duration of 24 weeks in genotype-1 infected patients should be strongly considered for patients who achieve RVR and have a baseline viral load below 800 000 IU/mL.

## DETERMINING RVR AT WEEK 4

Patients who are considered for shortened treatment duration must be tested at week 4 for RVR (i.e. no HCV RNA detectable) using a highly sensitive method (limit of detection ≤50 IU/mL) [15]. The week 4 value should be measured as close as possible to day 28 of therapy, i.e. between the fourth and fifth injection of peginterferon. Patients without assessment of RVR should not be considered as candidates for shortened therapy duration.

Monitoring is an important feature in the management of CHC; not only to document treatment success, but also as an indicator of compliance and adherence. Patients with RVR at week 4 should be tested again at week 12 (±5 days). The probability that the PCR test is negative at week 4 but positive at week 12 is low; only 1 of 22 patients who experienced virological breakthrough prior to week 24 had an RVR [40].

### *Optimizing response by reducing relapse rates in patients with HCV genotype 1*

A patient with virological relapse is one who achieved an end-of-treatment (EOT) response but who failed to achieve an SVR. Relapse has been reported to occur at similar rates for patients treated with peginterferon alfa-2a and -2b (18% and 19%, respectively) who were treated for 48 weeks according to the standard treatment algorithm [1,2]. The IDEAL study, which investigates response to peginterferon alfa-2a and two different doses of peginterferon alfa-2b with RBV in patients with genotype 1 CHC, is also addressing this issue [41]. Intensification of treatment is a possible approach to reduce the incidence of relapse. IDEAL is accepted as late-breaker at EASL 2008.

## INCREASED DOSE OF RIBAVIRIN

Recent studies suggest that high-dose RBV in combination with pegylated interferon can improve response in genotype 1-infected patients. Lindahl *et al.* used an individualized dosing regimen based largely on renal function, in an attempt to achieve >15 μmol/L steady-state RBV concentration in 10 treatment-naïve patients [42]. After initial dose adjustments, the mean dose of RBV was 2540 mg, qd (range 1600–3600 mg, qd) and the mean RBV concentration achieved was 14.7 μM (range 7.8–22.0 μM) at weeks 24–48. Nine of 10 patients achieved SVR following treatment of up to 48 weeks duration, but with more frequent and severe side effects, in particular anaemia. All patients required erythropoietin at some time during treatment.

A recent study by Fried *et al.* demonstrated an improvement in SVR in genotype 1-infected patients with body weight >85 kg treated with a higher dose of RBV, especially in conjunction with a higher dose of peginterferon [43]. Patients treated with 270 μg peginterferon alfa-2a and 1600 mg, qd, RBV showed an SVR of 47% compared with 28% in patients treated with the standard dosing regimen. This improvement was driven mainly by a marked reduction in relapse in the high-dose group compared with the standard-dose group (19% *vs* 40%, respectively). However, the use of a higher dose regimen was associated with an increased rate of haematological adverse events. More recently, in a prospective, open-label, randomized, controlled pilot study comparing 48 weeks of treatment with peginterferon plus standard weight-based RBV with or without erythropoietin (groups 1 and 2), and peginterferon plus higher weight-based RBV plus erythropoietin (group 3), SVR was significantly greater ($P < 0.05$) in group 3 patients (49%) due to a significant decline in relapse rate [44]. Overall, the results of these studies provide encouraging data regarding the possibility of optimizing treatment regimens for patients with more difficult to treat disease.

## EXTENDING TREATMENT DURATION FOR SLOW VIROLOGICAL RESPONDERS

Evidence from three randomized clinical trials support the case for extending treatment duration beyond 48 weeks in HCV genotype 1 patients with a slow virological response,

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