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REVIEW

Treatment extension benefits HCV genotype 1 patients without rapid virological response: a systematic review

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ABSTRACT

Background: Current guidelines recommend 48 weeks of treatment with pegylated interferon and ribavirin for patients infected with chronic hepatitis C virus (HCV) genotype 1. Several clinical trials have investigated the efficacy of treatment duration longer than 48 weeks, but yielded discordant results.

Methods: We performed a structured search of PubMed, Web of Science and the Cochrane library to identify randomised clinical trials in HCV genotype 1 patients who were treated either for 48 or 72 weeks. Sustained viral response (SVR) data were pooled and a sample size weighted pooled proportion was calculated.

Results: We identified five studies matching our criteria. Studies randomised at baseline (n=1), at absence of rapid virological response (RVR) at week 4 (n=1), at early virological response at week 12 (EVR) (n=1) or at slow response at week 24 (n=2). In the RCT that randomised at absence of RVR, SVR was significantly higher in the extended treatment arm (57 *vs* 42%, p=0.02) with an RR of 1.35 (95% CI 1.04 to 1.75). This tendency was also observed in the studies that randomised at slow response (44 *vs* 35%), although no longer statistically significantly different.

Conclusion: Prolonged 72-week treatment should be considered in HCV genotype 1 patients without RVR at week 4, as this increased SVR.

KEYWORDS

Hepatitis C, systematic review, antiviral therapy, treatment duration

INTRODUCTION

Infection with hepatitis C virus (HCV) is a significant cause of chronic liver disease.[1] It has been estimated that approximately 170 million people, 3% of the world's population, suffer from HCV infection and it is one of the main causes of chronic liver disease and indication for liver transplantation in the United States and in Europe.[2] Six distinct but related HCV genotypes and multiple subtypes have been identified on the basis of molecular resemblance, of which genotype 1 is most common in the US and Western Europe.[2] The probability of eradicating HCV depends on the genotype; and current treatments give better responses for genotypes 2 and 3, as compared with genotypes 1 and 4.[3,4]

The currently recommended treatment for patients infected with HCV genotype 1 is pegylated interferon (PEG-IFN), in combination with weight-based 800 to 1400 mg ribavirin daily, for 48 weeks.[5] Approximately 40 to 60% of patients achieve a sustained virological response (SVR) with this regimen.[3,4,6] The efficacy of treatment against HCV has improved, but is still far from ideal. It remains complex, is costly and has substantial side effects, which often lead to early discontinuation and consequent treatment failure.

This has led to the introduction of tailor-made therapy, a dynamic approach that individualises treatment on the basis of measurement of HCV viral load at given time points. In HCV genotype 1, patients with low viral load at onset and undetectable HCV RNA after four weeks of treatment (rapid virological response, RVR), 24 weeks of treatment is equally effective as standard 48 weeks.[7] For patients without RVR and with undetectable HCV RNA after 24 weeks of treatment, the situation is less clear.

The SVR rates in these patients are lower compared with the patients with RVR, even with treatment duration of 48 weeks. This has led to the hypothesis that longer treatment of up to 72 weeks may cure slow-responding HCV patients.

Recently, some clinical trials have investigated the efficacy of extending treatment duration to 72 weeks, but yielded discordant results.[8-12] Two prospective studies found significantly higher SVR rates with prolonged treatment compared with standard 48 weeks in HCV genotype 1 patients.[11,12] In contrast, three other trials have demonstrated that extending duration of treatment does not result in better SVR rates.[8-10] A systematic analysis of the data from these individual trials is necessary to address the issue and judge whether longer treatment indeed increases efficacy and which patients benefit from extended treatment.

The purpose of this systematic review is to evaluate different treatment duration regimes on achieving SVR and to make an evidence-based recommendation on the optimal length of treatment for HCV genotype 1 patients.

METHODS

Literature search

We followed the QUORUM guidelines for all steps reported in this systematic review.[13] A systematic literature search with predefined search terms was carried out in Medline (PubMed), Cochrane CENTRAL, Web of Science® and ClinicalTrials.gov for articles and abstracts published from 2000 until March 1, 2010.

The keywords 'HCV or hepatitis C', 'ribavirin or Rebetol® or Copegus®' and 'pegylated interferon, peginterferon, Pegintron® or Pegasys®' were combined. We used the following search limits: human; adults; randomised clinical trials; and English language.

Study selection

We selected prospective studies that evaluated standard pegylated interferon and ribavirin combination therapy in HCV genotype 1 patients and randomly compared extended (72 weeks) with standard (48 weeks) treatment duration. We adopted the following inclusion criteria: manuscripts written in English, adults (+18 years) with chronic HCV genotype 1, use of standard combination therapy similar in both arms, randomised controlled trials, availability of SVR rates in both arms, and the report was published in a book, journal, proceeding or indexed abstraction.

Exclusion criteria were studies referring to patients with HIV co-infection, hepatitis B virus co-infection, decompensated liver cirrhosis, hepatocellular carcinoma, haemophilia, and liver or renal transplantation. Studies that involved previously treated patients, relapsers or patients unresponsive to previous treatment were also excluded.

An additional search was performed using references of all included articles to retrieve eligible studies possibly missed by our systematic literature search.

Validity assessment

The quality of the randomised controlled trials (RCTs) was assessed and scored using the Jadad scale, which considers three items: randomisation (1 point if yes or 2 points if the method to generate the sequence of randomisation was described and appropriate), double blinding (1 point if yes or 2 points if the method of double blinding was described and appropriate) and description of withdrawals and dropouts (1 point).[14]

Data abstraction

Titles and abstracts of all retrieved records and subsequently full-text articles were examined independently by two investigators (TG and SS) to identify RCTs that satisfied the inclusion criteria. Discrepancies in selection were resolved by discussion between the authors of this systematic review.

All data from the selected studies were extracted using a standardised data collection form. The following characteristics were recorded: year of publication, study design, funding by pharmaceutical company, full text and population baseline characteristics (age, gender, body mass index, HCV viral load, fibrosis stage and ethnicity).

Data were separated and extracted for extended and standard treatment regarding the following: randomisation time point, number of participants per treatment arm, duration of treatment, dosages and type of pegylated interferon and ribavirin, end of treatment (EOT) and SVR.

Endpoints of interest

The primary outcome of interest in this systematic review was to explore SVR rates; we used the following definition: a negative result on a qualitative PCR assay for HCV RNA 24 weeks after the EOT. The secondary endpoint was EOT, defined as a negative result on a qualitative PCR assay for HCV RNA after termination of treatment (extended 72 weeks *vs* standard 48 weeks).

Statistical analyses

The effect of the two management strategies on SVR rates in HCV genotype 1 patients was expressed as a relative risk (RR) with a 95% confidence interval (CI) using the Mantel-Haenzel method. If possible, a sample size weighted pooled proportion and a pooled RR were calculated after data on SVR were pooled. The number needed to treat is calculated as 1 divided by the absolute risk reduction. Outcomes were analysed on an intention-to-treat basis. All data were pooled using a random effect

model, and statistical analyses were performed using Review Manager version 5.0.24 for Windows (provided by the Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Trial characteristics

We identified five potential RCTs matching our criteria, representing a total of 1267 HCV genotype 1 patients. All RCTs were published as full papers.[8-12] The selection of articles is depicted in *figure 1*. Maximal quality for the RCTs in this systematic review was a Jadad score of 3 points. All studies were open-label RCTs and described their dropouts and withdrawals.

The included studies differed in time of randomisation. We identified RCTs that randomised at baseline,[8] at absence of RVR at week 4,[12] at early virological response (EVR) at week 12 [10] or at slow response at week 24.[9,11] Detectable HCV RNA levels at week 4 and an undetectable HCV RNA at week 12 or a ≥2 log10 decrease from baseline serum HCV RNA was defined as an EVR. A slow responder was defined as a patient with at least a 2-log10 decrease in baseline serum HCV RNA at week 12 and undetectable serum HCV RNA at week 24. All non-responders at week 24 were excluded from analysis. Characteristics of the five studies and corresponding study populations are given in *table 1*. While the baseline characteristics of two studies also include data from patients with genotype 2, 3 or 4,[10,12] the majority of these populations comprised genotype 1 patients (>90%).

In two studies, the treatment regimen consisted of ribavirin and pegylated interferon-α2b of 1.5 μg/kg/week,[9,11] while in three studies pegylated interferon-α2a was administered at 180 μg/week.[8,10,12] In one study, patients assigned to the extended treatment group received a lower dose of pegylated interferon-α2a after week 48 (135 μg/week).[10] Ribavirin was given at a fixed dose of 800 mg daily in two trials [8,12] and at a body weight-based dosage of 800 to 1400 mg daily in three trials.[9-11]

Analysis of SVR rates

In the study that randomised at 4 weeks, patients without a virological response after 24 weeks of treatment were also included.[12] Therefore, non-responders (detectable serum HCV-RNA level at 24 weeks with a <2 log10 decrease from baseline) were excluded and a subgroup analysis was performed on 242 patients comparing extended (72 weeks) with standard (48 weeks) treatment duration *(figure 2)*. This study population also included patients with other genotypes; however, the majority of these patients were genotype 1 (˜ 90 %). The other trials all included exclusively genotype 1 patients. In the study by Sánchez-Tapias, SVR was significantly higher with

Figure 1. *Selection of articles*

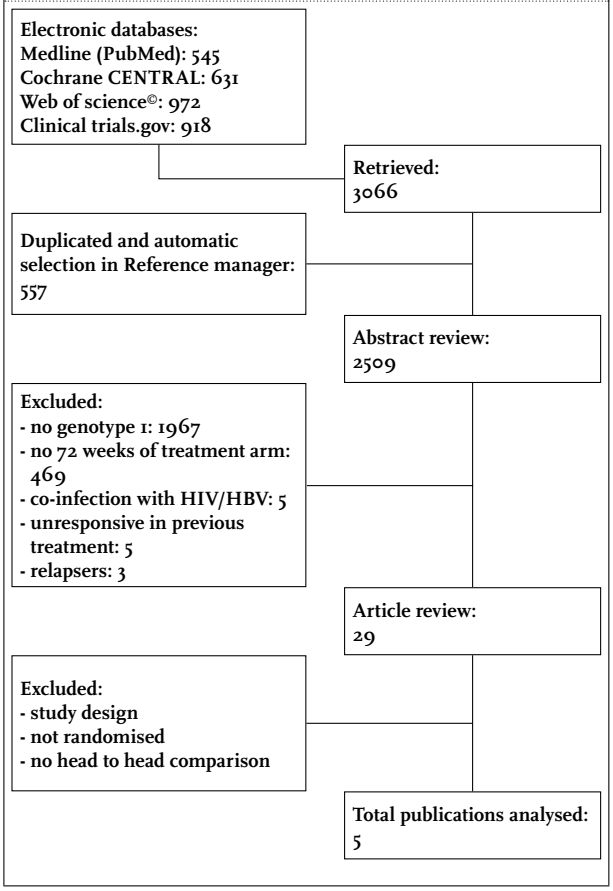
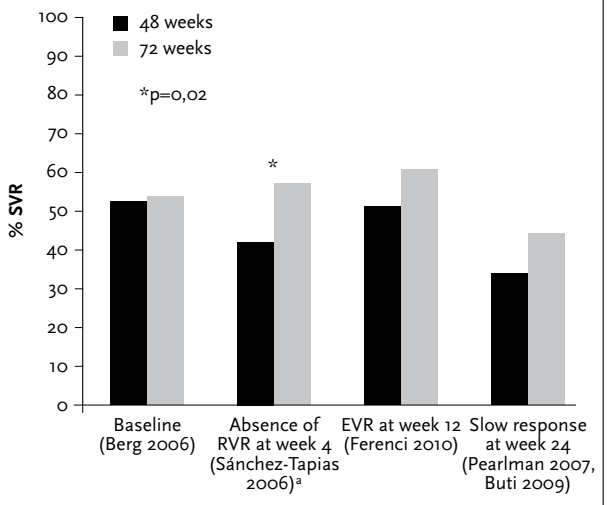


Figure 2. *SVR rates after standard versus extended HCV combination therapy of trials randomised at different time points*



[a]**Results of subgroup analysis with non-responders at 24 weeks of treatment excluded.**

Table 1. *Characteristics of the randomised controlled trials used in the systematic review of therapies on HCV genotype 1 patients*

Study	Patients, n	Randomisation	Industry funded	Jadad scale	PEG IFN	Ribavirin, mg	Mean age, years (±SD)	Male gender, n (%)	Mean BMI, kg/m² (±SD)	HCV viral load, x 10^6 IU/ml, mean (±SD)	Fibrosis/ cirrhosis Metavir score, n (%)	Ethnicity
Berg[8]	455	Baseline	yes	3	α2a	800	42.7 (11.4)	250 (54.9)	25.5 (4.2)	5.77 (0.52)	F3-4: 36 (8)	Caucasian
Sánchez-Tapias[12]	291	Absence of RVR	yes	3	α2a	800	43.0[a]	215 (66)[a]	24.7[a]	1.04[a]	NA	Caucasian
Ferenci[10]	261	EVR	yes	3	α2a	1000-1200	44.7[a]	188 (65)[a]	NA	0.67[a,b]	F3-4: 57 (20)[a]	Caucasian
Pearlman[11]	101	Slow response	no	3	α2b	800-1400	55 (25-66)[c]	67 (66)	28.9	5.3	F3-4: 26 (26)	Mixed
Buti[9]	159	Slow response	NA	3	α2b	800-1400	45.4 (10.7)	98 (61.6)	NA	6.59	NA	Caucasian

[a]Includes data of patients with other genotypes; [b]median; [c]mean (range). RVR = rapid virological response; EVR = early virological response; PEG-IFN = pegylated interferon; BMI = body mass index; HCV = hepatitis C virus; NA = not applicable.

72 weeks (57%) compared with the standard treatment (42%, p=0.02) with an RR of 1.35 (95% CI 1.04-1.75) and a number needed to treat (NNT) of 7 *(table 2)*.[12]

In the study that randomised at baseline,[8] no statistically significant difference was found for SVR rates at 48 (SVR 53%) or 72 weeks (SVR 54%) *(figure 2)*. In the study that randomised at EVR, higher SVR rates were observed with extended treatment when compared with standard treatment,[10] although the observed difference was not statistically significant (60 *vs* 51%).

One trial with a total of 101 patients randomised at slow response favoured longer (72 weeks, SVR 38%) treatment over standard (48 weeks, SVR 18%, p=0.026) treatment.[11] In contrast, a second trial studying 159 slow responders showed no statistically significant difference on effect of extended (48%) *vs* standard (43%) treatment.[9] We found a sample size weighted pooled proportion of 44% for 72 weeks and 35% for 48 weeks, corresponding with a pooled RR of 1.42 (95% CI 0.77 to 2.63) *(table 2)*.

Table 2. *Relative risks of SVR rates after standard versus extended HCV combination therapy of trials randomised at different time points*

Time point of randomisation	Study	RR (pooled)	95% CI
Baseline	Berg[8]	1.02	0.86-1.21
Absence of RVR	Sánchez-Tapias[12]	1.35	1.04-1.75[a]
EVR	Ferenci[10]	1.18	0.95-1.47
Slow response	Pearlman, Buti[9,11]	1.42	0.77-2.63

RR = relative risk; CI = confidence interval; RVR = rapid virological response; EVR = early virological response; [a]P = 0.02, standard treatment *vs* extended treatment.

Analysis of EOT rates

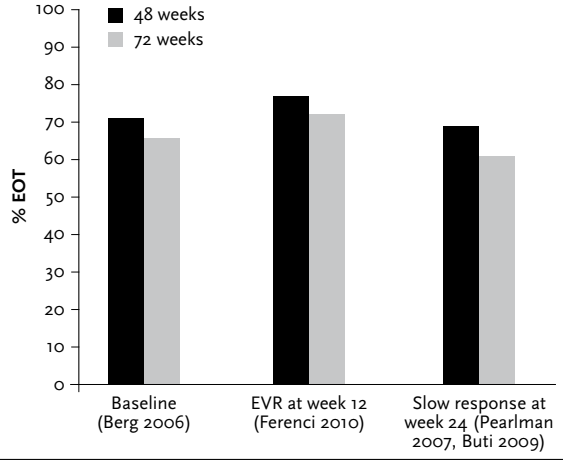
The EOT rates of the standard *vs* the extended treatment group were comparable in all trials *(figure 3)*. Slightly higher EOT rates were seen in the standard treatment group in the studies that randomised at baseline (71 *vs* 66%), at EVR (76 *vs* 72%) and at slow response (69 *vs* 61%).[8-11] No EOT rates were calculated in the subgroup analysis in the study by Sánchez-Tapias et al.[12] None of the observed differences were statistically significant.

All trials showed similar withdrawal rates related to serious adverse events among treatment arms.

DISCUSSION

The key finding of our systematic review is that HCV genotype 1 patients without RVR at week 4 may benefit

Figure 3. *EOT rates after standard versus extended HCV combination therapy of trials randomised at different time points*



from an extended combination therapy of 72 weeks. Furthermore, 72 weeks of combination treatment led to higher SVR rates in trials that randomised at baseline, at 12 weeks or at 24 weeks, although the difference was no longer statistically significant. For the latter studies, EOT rates were comparable in both arms. This suggests that the differences in SVR likely result from the proportion of patients who relapsed after the standard 48 weeks of treatment.

Due to the systematic design of our literature search with predefined inclusion and exclusion criteria, we only included randomised clinical trials that compared head-to-head standard *vs* prolonged treatment. Two interesting RCTs did not meet the inclusion criteria of our systematic review, as the length of the extended treatment in these trials was variable.[15,16] Patients in these studies received individualised treatment based on the time when HCV RNA first became undetectable instead of fixed treatment duration of 72 weeks and were not randomised in the variable treatment group. Nonetheless, our results are generally in line with the study by Mangia *et al.*[16] In a subgroup analysis of patients with EVR at week 12, substantially higher SVR rates were attained if the patient was treated for 72 weeks (63 *vs* 38%,), although this difference was not statistically significant (p=0.068). In the same line, these results were also found in the trial by Ferenci *et al.*, that randomised at EVR (60 *vs* 51%).[10] In this study, patients were included with both complete and partial EVR (detectable HCV RNA at weeks 4 and 12, with a ≥ 2-log10 decrease from baseline in serum HCV RNA at week 12), while the study by Mangia *et al.* only included patients with complete EVR. Patients with complete EVR have a higher probability of achieving an SVR than patients with partial EVR; therefore, we would expect lower SVR rates in the study by Ferenci *et al.*[17] However, the low number of patients in the subgroup analysis by Mangia *et al.* precludes definite conclusions.

Ide *et al.* showed that extending treatment by 44 weeks once HCV RNA levels first became undetectable significantly increased SVR rates in patients who were HCV RNA negative at 16 to 24 weeks.[15] This is in contrast with our results, because we did not find a benefit in extending treatment for patients with undetectable HCV RNA levels after week 12 (slow responders). Another finding in the study by Ide and colleagues was that patients with undetectable virus at week 8 and 12 had similar SVR rates in both treatment groups. This observation is consistent with our results; patients with an EVR at week 12 do not benefit from extended treatment.[10] Nevertheless, no definite conclusions about the value of this strategy can be drawn from this study due to small sample sizes.

In our systematic review, two trials were included that used a fixed dose of ribavirin of 800 mg/day instead of weight-based dosage regimens (800 to 1400 mg daily).[8,12] A previous study showed that low fixed dose of ribavirin (800 mg/day) was inferior to a higher weight-based dose of ribavirin (1000 or 1200 mg/day) regarding attaining SVR rates when treated for standard 48 weeks.[18] However, the optimal ribavirin dosage regimen for 72 weeks of treatment has not yet been elucidated. It is possible that suboptimal dosage of ribavirin in this study might have impacted more negatively on SVR rates when treated for 48 weeks of treatment than for the extended 72 weeks.[12] However, another RCT also used a suboptimal dose of ribavirin (800 mg/day) and did not find this difference in SVR rates.[8] The observed difference in SVR rates between these two trials could be caused by the mixture of rapid and slow virological responders in one trial.[8] We found similar SVR rates among trials that used weight-based dosages.[9-11]

In the included trials, two types of pegylated interferon (α2a and α2b) were investigated in combination with ribavirin. Current evidence suggests that peginterferon α2a is associated with higher SVR than peginterferon α2b.[19] Both trials that randomised at slow response used pegylated interferon α2b, while the other trials used pegylated interferon α2a. The results of trials using pegylated interferon α2a cannot be extrapolated to patients using pegylated interferon α2b and vice versa, due to these differences in pharmacokinetic profiles. Furthermore, in one study a lower dose of pegylated interferon-α2a was given after week 48 (135 μg/week). This suboptimal dose of pegylated interferon may lead to lower SVR rates, although this has not been formally proven in randomised clinical trials. [10]

One study did not require patients with detectable HCV RNA at week 24 to discontinue further treatment.[12] According to protocol, patients with detectable HCV RNA at 24 weeks are regarded as non-responders and should therefore be excluded from further treatment.[5] This study also performed a subgroup analysis on patients with an undetectable serum HCV RNA level or a ≥2 log10 decrease from baseline in serum HCV RNA levels at 24 weeks of treatment, thereby excluding the non-responders. Ten percent of this study population consisted of patients with genotype 2, 3 or 4. It is possible that the observed difference in SVR rates between 48 and 72 weeks of treatment could be explained by the proportion of patients with genotype 2 and 3, patients known to have better treatment responses, in both treatment groups. However, due to the low proportion of patients with genotype 2 and 3, eight in the standard treatment group and nine in the extended treatment group, respectively, this effect is negligible.

The main strength of our study is that we systematically analysed all RCTs that compare duration of therapy in HCV genotype 1 patients. Although included RCTs use different times of randomisation, we provide an overview

for clinicians faced with the difficult decision-making in treating patients with HCV genotype 1. Another strength of this systematic review was that all included trials had a sizeable number of genotype 1 patients and that the number of patients were comparable in all studies. Our systematic review comes with some limitations. First, this systematic review only focuses on timing of viral response as a key success factor. We know that genetic variants of IL-28B are strongly associated with the response to HCV treatment. Indeed, the beneficial (CC) IL-28B genotype is associated with improved early viral kinetics and greater likelihood of RVR, complete EVR, and SVR.[20] Secondly, because of the heterogeneity in study design of the included trials, we were unable to analyse potentially important predictors of outcomes such as race, severity of baseline disease and body mass index due to inaccessibility of individual patient data.

Our study provides important information for clinicians treating HCV genotype 1 patients. Absence of RVR at week 4 is an important parameter in determining the success of extending treatment to 72 weeks. Although abbreviated regimens have tolerability advantages, are less expensive and reduce exposure to side effects, less relapse occurs with prolonged treatment. Furthermore, extending treatment does not lead to higher withdrawal rates due to serious adverse events. If compliance of patients assigned to 72 weeks can be improved, the probability of attaining SVR rates can be further maximised. On the other hand, patients assigned to 72 weeks of treatment have higher dropout rates compared with patients in standard treatment groups and are less likely to be cured, thereby possibly increasing costs. Furthermore, if all non-RVR patients are treated for 72 weeks, costs of treatment will increase. Therefore, even if extending treatment duration to 72 weeks should yield better SVR rates, it still needs to be determined whether this prolongation is cost-effective.

In conclusion, this systematic review demonstrates that in HCV genotype 1 patients without RVR at week 4, treatment extension with pegylated interferon and ribavirin to 72 weeks increased SVR significantly. However, the consequence for current daily practice is unclear as the ribavirin dosage now used is higher and the optimal ribavirin dose for 72 weeks of treatment has not been determined yet. Furthermore, in slow responders the standard duration of treatment should still be 48 weeks, although a beneficial effect of 72 weeks of combination treatment could not be excluded. Prolonging treatment duration to 72 weeks might be considered in HCV genotype 1 patients who do not reach RVR at week 4.

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