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Journal of Hepatology 51 (2009) 675–681
Journal of Hepatology
www.elsevier.com/locate/jhep

Retreatment with pegylated interferon plus ribavirin of chronic hepatitis C non-responders to interferon plus ribavirin: A meta-analysis☆

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***Background/Aims*: Efficacy of retreatment with pegylated interferon (PEG-IFN) plus ribavirin of non-responders to standard or pegylated IFN plus ribavirin has been assessed in various studies, but sustained virologic response (SVR) rates are variable and factors influencing efficacy and tolerability still remain incompletely defined. We aimed to focus on SVR rates and to identify factors influencing them in this meta-analysis.**

***Methods*: MEDLINE as well as a manual search were used. Studies were included if they were controlled or uncontrolled trials, if they had been published as full-length papers and if they included non-responders to standard or pegylated IFN and ribavirin therapy. Fourteen trials were included in the meta-analysis. Data on study populations, interventions, and outcomes were extracted from trials using a random-effects model. Primary outcome was the SVR rate.**

***Results*: The pooled estimate of SVR rate was 16.3% (95% Confidence Interval – 95% CI, 8.3–29.6%). There was a significant heterogeneity among studies ($p < 0.0001$). Heterogeneity was less apparent in studies that included fewer patients with cirrhosis or overweight. By meta-regression, higher SVR rate was observed in trials with a lower prevalence of subjects with genotype 1 infection and with fewer overweight patients. The use of a 24-week retreatment stopping rule did not affect SVR rate.**

***Conclusions*: The overall modest efficacy argues against an indiscriminate retreatment with PEG-IFN and ribavirin of all non-responders. Restricting retreatment to non-overweight patients or to those with genotype 2 or 3 infection, using a 24-week retreatment stopping rule, would optimize the potential benefit with a scarce likelihood of missing a curative response.**

***Keywords*: HCV; Interferon; Sustained virologic response; Ribavirin**

Received 9 April 2009; received in revised form 19 June 2009; accepted 22 June 2009; available online 15 July 2009
Associate Editor: M. Colombo

☆ The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Abbreviations: HCV-RNA, hepatitis C virus ribonucleic acid; SVR, sustained virologic response; PEG-IFN, pegylated interferon; IFN, interferon; NR, non-responder; HCV, hepatitis C virus.

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doi:10.1016/j.jhep.2009.06.018

1. Introduction

Since the early 2000s, at least 50% of patients with chronic hepatitis C treated with standard α interferon (IFN) and ribavirin combination therapy have not responded to therapy. A large cohort of non-responders (that is, subjects with detectable hepatitis C virus RNA [HCV-RNA] 3 or 6 months after initiation of therapy) thus exists within the pool of subjects with chronic hepatitis C. The clinical course of the disease can be more severe in these patients, with an accelerated progression towards end-stage liver disease [1] and development of hepatocellular carcinoma [2]. Therefore, an effective regimen of retreatment is a major goal in the long-term management of these patients.

Several studies of retreatment with pegylated IFN (PEG-IFN) plus ribavirin in patients who failed to respond to the combination of pegylated and non-pegylated IFN plus ribavirin have been published [3–22]. The results of these studies are inconclusive or conflicting because of the relatively small samples and the differences in patient characteristics, study design combining relapsers and non-responders, doses of IFN and ribavirin administered in the first course, and retreatment regimens.

Although the American Association for the Study for Liver Disease (AASLD) Practice Guidelines recommend that retreatment with PEG-IFN plus ribavirin be considered for non-responders who have undergone previous regimens of combination treatment using non-pegylated interferon [23], important questions still remain unanswered. Is retreatment with PEG-IFN plus ribavirin useful in all non-responders to the combination? Are there any differences in the effectiveness of retreatment between different HCV genotypes, between cirrhotic and non-cirrhotic patients and between different retreatment regimens? How useful might it be to prolong retreatment up to 48 weeks also in patients who have failed to clear HCV RNA by week 24?

To increase statistical power and to resolve uncertainty we propose a meta-analysis of the available studies. The aims of this meta-analysis are: (1) to assess the efficacy and tolerability of retreatment in obtaining SVR; (2) to analyze the variability in SVR rates by looking at the heterogeneity among the studies as a means of interpreting this variability; and finally, (3) to identify possible predictors of SVR.

2. Materials and methods

2.1. Selection of trials

This analysis was performed in accordance with the QUOROM statement [24]. Retrieval of trials was based on the Cochrane Controlled Trials Register, The Cochrane Library, MEDLINE and EMBASE, using the following medical subject headings: *chronic hepatitis C, non-responders, interferon and ribavirin, pegylated interferon, retreatment*, and *clinical trial*. The search was carried out in April 2009 without a lower date limit on the search results. The computer search was supplemented with manual searches for reference lists of all retrieved review articles, primary studies and meeting abstracts in order to identify other studies not found in the computer search.

Studies were included if they were randomized controlled trials or prospective cohort studies, if they had been published or accepted for publication as full-length papers, if they included patients with chronic hepatitis C who were non-responders to standard or pegylated IFN and ribavirin combination therapy who were retreated with pegylated IFN plus ribavirin, and if non-response was defined as detectable serum HCV-RNA 3 or 6 months after initiation of therapy. In order to assess publication bias we researched also for abstracts. Excluded studies were identified with the reason for exclusion.

Of the 226 references identified through a MEDLINE search, 184 were excluded upon analysis of the abstract because they did not meet inclusion criteria. Of the remaining 42 full-text articles, 30 were excluded because they did not meet inclusion criteria, leaving 14 full-length papers [3–16] meeting criteria for inclusion in the meta-analysis. Finally, 6 abstracts identified by manual search [17–22], were also included, only for the evaluation of the publication bias.

2.2. Review of the trials

The trials were first reviewed using a list of predefined, pertinent questions that concerned the characteristics of patients, treatments, outcomes and study validity. Each trial was evaluated and classified by three independent investigators (F.B., A.L., G.C.). Discrepancies among reviewers were infrequent (overall inter-observer variations <10%), and were resolved by discussion. The methodological quality of the studies was assessed by four principal criteria, as listed in Table 1 in Appendix. Each quality component was rated as yes or no. The quality of trials was reported according to each separate component. Since none of the trials met all quality criteria (see Table 1 in Appendix), "good quality" studies were arbitrarily defined as those that fulfilled 2 of the 4 principal quality criteria.

2.3. Statistical analyses

Pooled estimates of SVR were calculated using random-effects logistic regression analysis after applying sample weights according to the sample size, using SAS version 8.1 (SAS Institute, Cary, NC, USA) software, PROC NLMIXED command. Heterogeneity among studies was assessed with the Pearson $\chi^{2\text{-test.}}$ The assumption of heterogeneity implied by the utilization of random-effect models is justified by the differences in patients' features and study characteristics. A recommended approach to dealing with heterogeneity is sorting the heterogeneous group of studies into subgroups according to a stratifying variable suspected of having caused the inconsistency. Therefore, stratum-specific rates of the SVR rates for different patient-level and study-level covariates were calculated. We used 11 stratifying variables: type of publication, number of participating centers, study sample size, mean age, percentage of males, mean BMI, percentage of genotype 1 infected subjects, percentage of cirrhotic patients, type of pegylated interferon, dose of ribavirin, and study validity.

Only univariate logistic regression analyses were used to examine the association between features of the study and the SVR rates. We did not consider multivariate analysis because of the wide heterogeneity and lack of complete data for identification of possible variables that could explain heterogeneity.

Begg's funnel plots were generated and Egger's [25] regression asymmetry test was used to examine potential publication bias related to the SVR rate. For all analyses, a p of <0.05 was considered statistically significant. All analyses were completed with SAS version 8.1 (SAS Institute, Cary, NC, USA) software.

3. Results

3.1. Description of the studies

After review of the titles, 14 full papers fulfilled the inclusion criteria and were selected for review. The main

features of the trials included in the meta-analysis are shown in Table 2 in Appendix. Fourteen, which accounted for 3898 patients, were reported as full papers [3–16]. Among the trials, three studies did not report the number of participating centers, while all remaining studies were multicenter trials, with the number of centers ranging from 2 to 133; among these studies 8 reported data on the prevalence of patients with cirrhosis (357/1282 = 27.8%). Regarding the design of the study, 13 were prospective cohort studies while only 1 was RCT [16].

The percentage of males ranged from 60% to 84%. The sample size of each study varied greatly, ranging from 20 [14] to 1385 [15] patients. Mean patient age was 47.8 years, ranging from 41.8 to 50.2. The proportion of patients with cirrhosis ranged from 0% to 39%. Data on the proportion of patients infected by genotype 1 were lacking in 4 trials and was high in all the studies that reported this rate, ranging from 71% to 100%. Among the full-length papers, four studies did not report the body mass index (BMI). The average value of BMI among the studies was 27.5 K/m^2. The first treatment schedule was reported in five studies only [6,8,10,11,15], showing a large variability in the doses of standard IFN and ribavirin administered.

Among the 14 full-length papers, 7 studies defined non-response as detectable serum HCV-RNA 3 months after initiation of therapy, 5 studies as detectable serum HCV-RNA 6 months after initiation of therapy, while in two studies the timing of HCV-RNA detection was not reported.

With regard to the quality of the studies, the least commonly fulfilled quality criteria were enrolment of consecutive patients (10%), intention to treat analysis (40%) and absence of case mix of non-responders to IFN mono-therapy and to IFN plus ribavirin therapy (40%) (Table 1 in Appendix). In 6 out of 14 studies (43%), both non-responders and relapsers were included. Eight studies [3,4,6–9,13,16] met our definition for a "good quality study," i.e. they fulfilled 2 or more of the four principal pre-defined quality criteria (Table 1 in the Appendix).

3.2. Sustained virologic response rate

The therapeutic regimens of retreatment and the rate of SVR of the studies are shown in Table 2 in Appendix. A large variability of the retreatment regimens among trials was found in the type of Peg-IFN (α-2a or α-2b); the dose of Peg-IFN α-2b (ranging between 50 and 300 μg/week); and the dose of ribavirin (ranging between 800 and 1400 mg/die). In all but one [16] of the trials the length of retreatment was 48 weeks.

The SVR rate of the different studies is shown in Fig. 1. The 14 studies included 3898 patients. The pooled estimate of the SVR rate was 16.3% (95% CI, 8.3–29.6%). We found a remarkable heterogeneity in the magnitude of the treatment effect among the 14 studies (χ^2 for heterogeneity 159.5 with 19 DF; $p < 0.0001$). The proportion of patients who achieved an SVR differed greatly among the studies, ranging from 7% [5] to 30% [10]. A pooled analysis that excluded both these outliers, reporting the highest [10] and lowest [5] benefit of retreatment, yielded similar results (SVR 15.4%, 95% CI, 8–30%). The analysis of the remaining 13 studies, after omission of the RCT that included non-responders to a first course of pegylated interferon plus ribavirin [16], resulted in a similar effect size (SVR 15.8%, 95% CI, 6.2–33%).

Data on the SVR rate according to genotype infection (genotype 1 vs. genotype non-1) were reported in 7 trials only [6–9,11,12,15]. The pooled estimate of the SVR rate in the subgroups of these 7 studies was 15.6% (95% CI, 12.4–19.4%) for genotype 1 and 33.9% (95% CI, 25.8–43.1%) for patients infected by a genotype non-1 ($p = 0.0001$).

Since the 14 studies showed a marked heterogeneity, stratified analyses were carried out in relation to type of publication (full papers vs. abstracts), year of publication (2003–2005 vs. 2006–2009), sample size (⩽100 vs. >100 patients), number of participating centers (⩽13 vs. >13), mean age (⩽49 vs. >49 years), percentage of males (⩽73% vs. >73%), mean BMI (⩽28 vs. >28 Kg/m^2), percentage of genotype 1, (⩽80% vs. >80%), percentage of cirrhosis (⩽20% vs. >20%), type of Peg-IFN, (α-2a or α-2b) ribavirin dose (⩽800 vs. >800 mg/die), 24-week treatment-stopping rule (used vs. not used), and study validity (high quality vs. low quality) (Table 3 in Appendix).

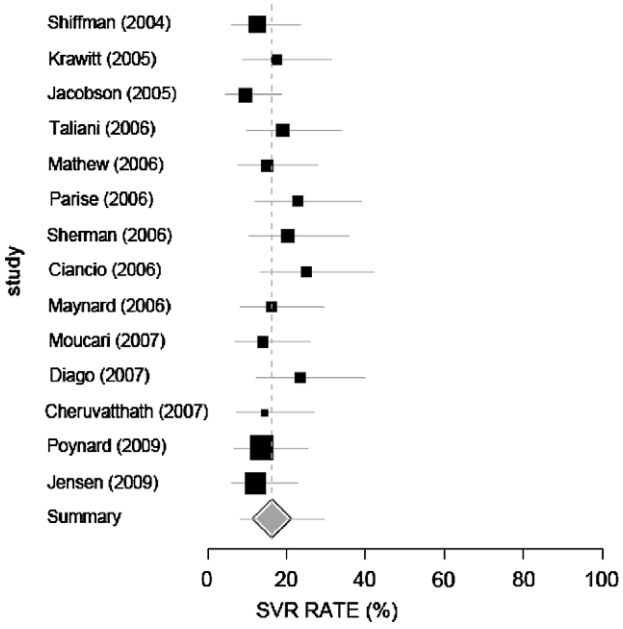

Fig. 1. Forest plot of sustained virologic response rates in 14 full-length papers.

To examine whether there were differences within each stratum of relevant study features, we next calculated pooled estimates of the SVR rate within each stratum and evaluated heterogeneity among strata. High (>20%) SVR rates were observed when assessing data pooled from studies including: (a) fewer than 100 patients; (b) patients with a mean baseline BMI ⩽28 Kg/m^2; (c) a percentage of genotype 1 ⩽80%; (d) a percentage of patients with cirrhosis of < 20%; and (e) patients retreated with PEG-IFN α-2a (Table 3 in Appendix).

Similar SVR rates were observed when comparing data pooled from studies that included patients who discontinued therapy at week 24 (SVR rate = 13.4%; 95% CI, 5.0–30.9%) to studies that included patients who completed 48 weeks of therapy (SVR rate = 16.7%; 95% CI, 7.2–34.1%). No difference in the magnitude of the treatment effect was observed between low quality studies (SVR rate = 16.7%; 95%CI, 13–21.1%) and high quality studies (SVR rate = 13.3%; 95%CI, 8.7–19.8%).

Heterogeneity was less evident in studies in which the sample size was ⩽100, in which the number of participating centers was ⩽13, in which the percentage of patients with cirrhosis was <20%, and in which the mean baseline BMI was ⩽28 Kg/m^2 (Table 3 in Appendix). Heterogeneity persisted in all the remaining strata.

Logistic regression analysis was used to identify potential sources of heterogeneity among the studies. Using univariate meta-regression, among the 12 variables assessed, only three variables were significantly associated with an increased rate of SVR: low mean baseline BMI ($p = 0.0005$), low percentage of patients with genotype 1 infection ($p = 0.005$), and treatment with Peg-IFN α-2a ($p = 0.029$).

4. Safety

Retreatment with a course of 48 weeks of Peg-IFN and ribavirin was not universally tolerated. Overall, side effects leading to withdrawal from both Peg-IFN and ribavirin retreatment occurred in 450 out of 3898 patients (11.6%; 95% CI, 10.5–12.6%) while 686 patients (17.6%; 95% CI 16.4–18.9%) required dose reduction of one or both drugs. Serious or life threatening (grade 3 or 4) adverse events were observed during treatment in 278 out of 3385 patients (7.1%; 95% CI, 6.3–8.0%). The distribution of the rate of adverse effects leading to withdrawal from therapy of patients who required dose reduction and of those who complained of grade 3 or 4 adverse events is shown in Fig. 2.

5. Publication bias

The plots and the Egger test for publication bias for full papers and abstracts showed that the risk of having missed or overlooked trials was not significant: the p value was 0.52 with the Egger test. This implies that small studies with low SVR rates were as likely to be published as large studies with high SVR rates. Similar results were obtained when abstracts were excluded from the analysis ($p = 0.74$).

6. Discussion

This meta-analysis of data from 14 studies, comprising nearly 4000 non-responders to combination therapy, showed that retreatment with a course of 48 weeks of PEG-IFN plus ribavirin achieves an SVR in 16% of patients with a 12% withdrawal rate due to adverse reactions or intolerance to drugs. Although the number of retreated patients in the available studies was high, suggesting that estimate of the cumulative SVR rate could be robust, the confidence intervals of the effect were wide (8.3–29.6%) due to the heterogeneity of the trials.

Our analysis demonstrates that heterogeneity of the SVR rate after retreatment is a feature of these studies and that it persists even in the stratum of high quality studies, implying that the large variability of the clinical

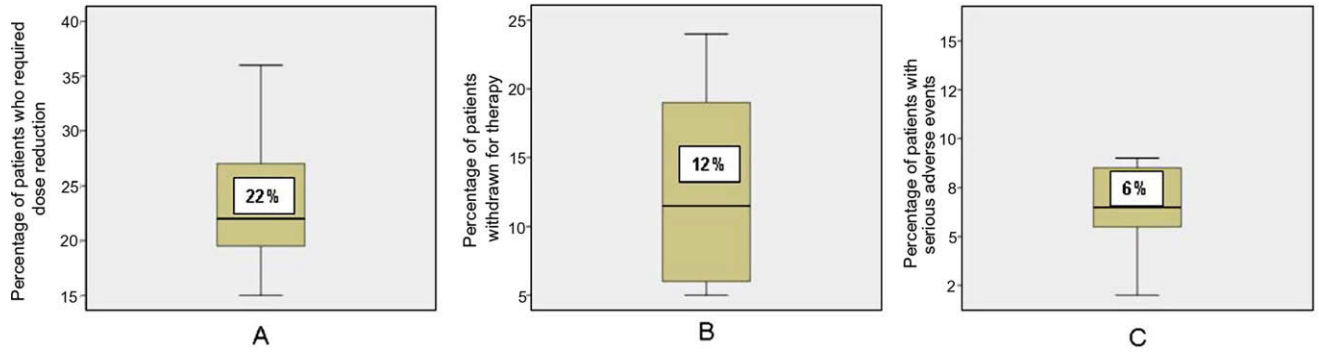

Fig. 2. Box plot for patients who: (A) required dose reduction, (B) withdrawn from therapy, (C) developed serious adverse events, expressed as a percentage. The middle horizontal line in each box is the median, the upper and lower line in each box indicate inter-quartile range, and the whisker indicates 90 percentile ranges.

benefit is not explained by study validity. The inconsistency in the SVR rate reported among trials is not surprising if one considers differences in design and power of the studies, potential biases in the selection of patients with different demographic, clinical and virologic characteristics, the variability in the doses of standard IFN and ribavirin, and the different treatment stopping rule of the first course of therapy. Interestingly, heterogeneity disappeared in studies with a sample size $\leqslant$100 patients, as well as in multicenter trials with few participating centers, suggesting that complex therapies need careful consideration before they can be routinely translated from large multinational trials into practice. A large variability in the SVR rates was also observed in studies that included more patients with cirrhosis or overweight, indicating that a population with advanced fibrosis and/or metabolic abnormalities is more heterogeneous in terms of likelihood of achieving an SVR.

The low overall efficacy and tolerability of retreatment, even in the most responsive strata, as well as the ensuing poor cost effectiveness, do not lend support to an indiscriminate retreatment of all non-responders to combination therapy, as only a minority of non-responders will eventually benefit from retreatment with pegylated interferon plus ribavirin.

In our analysis, the benefit of retreatment on the SVR rate was much more pronounced and statistically significant in patients with genotype non-1 infection, while we failed to find an improvement of the SVR rate in the subgroup of patients with genotype 1 infection. Hence the benefits of retreatment may outweigh the risks for patients with genotype 2 or 3 infection, whereas the risks may outweigh the benefits for patients with genotype 1 infection. However, data on the SVR rate according to different genotypes were lacking in several trials, and caution must be exercised when interpreting results from subgroup exploratory analyses.

Our analysis showed that studies that included patients with normal baseline BMI, and low prevalence of genotype 1 infection, and in which pegylated IFN α-2a was administered, showed a higher SVR rate. Although the mechanisms responsible for the effect of BMI on the SVR rate are unknown, a practical recommendation to reduce body weight before starting retreatment might achieve better SVR rates upon retreatment.

The slightly higher SVR rate observed when non-responders were retreated with pegylated IFN α-2a rather than pegylated IFN α-2b could be related to a spurious association due to ecological bias. This meta-analysis is not designed to find an explanation to this association, perhaps only a direct comparison, such as the IDEAL study of treatment-naïve patients [26], could resolve this question.

We failed to find a significant difference in stratum-specific SVR rates when comparing data pooled from studies with high and low prevalence of cirrhotic patients. However, our meta-analysis included a small sample of patients with cirrhosis, hampering any firm conclusion on the effect of advanced fibrosis on the likelihood of SVR.

Treatment discontinuation, treatment dose modification and serious adverse events occurred at extremely variable rates in the trials included in the meta-analysis. There was considerable variation in the dose of pegylated IFNs and ribavirin among the studies we evaluated, suggesting that standardized regimens are needed to obtain comparative data on efficacy and safety, particularly regarding the ribavirin dose. In our study, stratified analysis by ribavirin dose failed to indicate a significant difference in the SVR rate between high and low dose of ribavirin retreatment. Recently, a large multicenter RCT [16] showed that retreatment with a regimen of pegylated α-2a 180 μg/week plus ribavirin 1000/1200 mg/die for 72 weeks produced a significantly better SVR than high-dose short duration therapy (360μg/week for 48 weeks), at the cost, however, of significantly more intolerance to treatment. Since in all the studies included in this meta-analysis a conventional course regimen of 48 weeks was administered, we believe the available information is inadequate to determine whether a longer course of standard-dosage (180 μg/week for 72 weeks) could achieve better results than a conventional course of standard-dose (180μg/week for 48 weeks). Further large-scale multicenter RCTs will prove useful in substantiating the benefit of retreatment of non-responders with a prolonged course of therapy.

We found no confirmation of Taliani and colleagues' observation [6] that a prolongation of therapy beyond 24 weeks in HCV RNA-positive patients may further increase the rate of SVR. Our meta-analysis provides evidence that similar SVR rates were observed when data pooled from studies discontinuing therapy at week 24 were compared to those continuing therapy to 48 weeks. So, in line with what has been observed in treatment-naïve patients treated with the same regimen, we do not recommend prolonging to 48 weeks the retreatment of patients who failed to achieve virologic response by week 24. Moreover, based on the results of the trial by Poynard et al. [15] and of the trial by Jensen et al. [16] showing that patients with detectable HCV RNA at week 12 were unlike to achieve SVR, the treatment stopping role could be anticipated at week 12.

The results of this retrospective analysis are subject to several limitations. Differences in the design, in the sample, in the baseline severity of illness in the population of the studies, and in the re-treatment regimens may limit the accuracy of this meta-analysis. We attempted to control for these differences by including covariates that described the patients studied and the study design features. Lack of data on other potential confounders, such as the dose of standard IFN and ribavirin administered during the initial course, could also affect the accuracy

of the results. The meta-analysis was performed using summary data, and more detailed treatment comparisons could be made with a meta-analysis of individual patient data (MIPD). However, it was documented the increase in time and cost required by MIPD over study-level analysis. In addition, it may not always be possible to obtain IPD from all the studies, raising the issue that the studies for which data are available may represent a biased subset of the available studies.

As with all meta-analyses, this study also has the potential limitation of the generalizability of results to new populations and settings. Meta-analyses are likely to have poor external validity when the included studies all use the same limited patient population or are all conducted in a single setting. As non-responders are a heterogeneous population, we decided to include studies with different designs particularly nonrandomised trials conducted in real clinical practice and those that included non-responders to different first IFN courses retreated with different regimens. We believe that this approach may have improved the generalizability of our data to results observed in real clinical practice.

Finally, we are confident that publication bias was not substantial and, therefore, unlikely to change the direction of our pooled estimate of treatment effect and that the quality of individual trials seemed not to bias the results of our meta-analysis.

What are the implications of this meta-analysis for current practice? Concerning retreatment with a 48-week course of pegylated IFN plus ribavirin of non-responders to standard or pegylated IFN and ribavirin combination therapy the available evidence is sufficient to conclude that: 1) the modest overall efficacy and tolerability, and the inconsistency in the reported SVR rates amongst trials, argue against indiscriminate retreatment for all non-responders; 2) restricting retreatment to non-overweight patients or to those with genotype 2 or 3 infection optimizes the potential benefit; 3) due to its low probability of clinical benefit the decision to retreat subjects infected with HCV genotype 1 should be assessed in the individual patient according to the likelihood of disease progression and of adverse events; and 4) stopping treatment in HCV RNA-positive patients at 24 weeks is to be recommended.

Acknowledgement

The authors thank Warren Blumberg for his help in editing the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jhep.2009.06.018.

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