

# REVIEW ARTICLE

## Optimizing Treatment with Pegylated Interferon-Ribavirin of Genotype 3 Chronic Hepatitis C: More Questions than Answers

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Hepatitis C virus (HCV) is the foremost cause of parenterally transmitted non-A, non-B hepatitis. Effective treatment with Interferon (IFN) based regimens has been shown to reduce morbidity and mortality, improve health-related quality of life, and avoid the huge costs associated with end stage liver disease. HCV-3 has been associated in Europe and the USA to illicit drug abuse in the 70's, while recent epidemiological reports have shown that HCV-3 prevalence is on the rise in both Western Europe and in Middle East. The standard of care for patients with HCV-3 is a 24 week therapy regimen with a combination of Pegylated Interferon (Peg-IFN) and Ribavirin (RBV). Despite the cumulative high rates of sustained virological response (SVR) obtained with this schedule of treatment, it is now clear that a subgroup of patients exists in which lower rates of SVR are achieved. Bridging fibrosis/cirrhosis, high baseline viremia and lack of rapid virological response (RVR) have been identified as predictors of treatment failure in many studies. Recently, "allocation" and randomization trials based on HCV-RNA negativity at week 4 (RVR) have evaluated the chance of abbreviating the treatment schedule to 12-16 weeks, since RVR emerged as a strong predictor of SVR. In this review article we will discuss the current therapeutic strategies in HCV-3 to understand in which subset of patients further treatment customization is possible.

**Keywords:** Chronic Hepatitis C, Pegylated interferon, Ribavirin, Treatment

### Introduction

Hepatitis C virus (HCV) is the primary cause of parenterally transmitted non-A, non-B hepatitis <sup>(1, 2)</sup>. Chronic infection is associated with a lifetime risk of liver fibrosis, cirrhosis and hepatocellular carcinoma <sup>(3, 4)</sup>. Effective treatment with Interferon (IFN)-based regimen has been shown to reduce morbidity and mortality, improve health-related quality of life, and avoid the huge costs associated with end-stage liver disease <sup>(5)</sup>. Antiviral therapy for the treatment of HCV infection has evolved in recent years from IFN monotherapy to combination therapy with IFN and Ribavirin (RBV), to the present standard of care, namely Pegylated IFN (Peg-IFN) and RBV <sup>(6, 7)</sup>. Among the several factors that have become evident as predictors of response to antiviral therapy, HCV genotype is the most important viral factor <sup>(8-10)</sup>. Worldwide, HCV circulates as 6 major genotypes which are characterized by a different sensitivity to IFN and typical geographic distribution <sup>(11)</sup>.

HCV-3 has been associated in Europe and the USA to illicit drug abuse in the 70's, and is

considered to have spread from the Indian subcontinent. Recent epidemiological reports have shown that HCV-3 prevalence is on the rise in both Western Europe and in the Middle East, with immigration being the main culprit and intravenous drug users (IDUs) remaining at the core of HCV-3 ongoing epidemic phase <sup>(12-14)</sup>. Infection by drug abuse is, in fact, the most frequent route for HCV transmission, with 50-90% of users having been infected after 5 years of illicit use of intravenous drugs. As a consequence, HCV-3 together with genotypes 1a and 4 has replaced the more common

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**Received:** 3 Jul 2008

**Revised:** 10 Sep 2008

**Accepted:** 15 Sep 2008

**Hep Mon 2008; 8 (4): 304-309**

genotypes 1b and 2, spreading into Europe, among IDU and over the general population of HCV infected, probably by unsafe medical procedures, sexual exposure and vertical transmission<sup>(15, 16)</sup>.

From a therapeutic standpoint, HCV genotypes 2 and 3 have long been considered as "easy to treat" genotypes, being associated with significantly higher rates of sustained virological response (SVR) compared to genotypes 1 and 4<sup>(8-10)</sup>. In fact, patients infected with HCV-2 and HCV-3 achieve SVR rates of 70-90% following 24 weeks of treatment, in contrast with those infected with HCV-1 and HCV-4 who need 48 weeks of therapy to achieve an SVR rate of roughly 40-50%. Although a precise biological explanation for the different SVR rates among genotype 1 vs. genotypes 2 and 3 remains elusive, it has been clearly demonstrated that viral kinetics in response to IFN therapy play an important role; and despite the difference in the first and the second phase of decline, the viral decline among "easy to treat" genotypes is up to eight times faster than that observed in other genotypes<sup>(17, 18)</sup>.

As a consequence of their favourable response to antiviral therapy, genotypes 2 and 3 infections have frequently been grouped together when it comes to analyzing the efficacy data of clinical trials. However, more recent studies suggest that this practice should be abandoned and that data derived from HCV-2 patients should not be extrapolated to HCV-3 patients since HCV-3 shows a different pattern of response to Peg-IFN and RBV than HCV-2 which ultimately translates into lower SVR rates after a 24 week treatment course<sup>(19)</sup>.

In this article we will review the available current knowledge on the treatment of HCV-3, and analyze how treatment can be further customized in this subgroup of patients.

## Materials and Methods

A systematic literature search using the PubMed citation database from 2001 to 2008 was performed to identify English-language articles based on the efficacy of antiviral therapy among patients infected with HCV-3 by using the following terms alone or in combination: Interferon, Peg-Interferon, Ribavirin, HCV, genotype 3, genotype 2, antiviral therapy, Sustained Virological Response (SVR), Rapid Virological Response (RVR), abbreviated therapy. Reference lists of all identified articles were checked for relevance.

We included all the studies evaluating abbreviated treatment schedules but only the prospective and

retrospective studies in which data of HCV-3 patients could be extrapolated from those with HCV-2.

As a policy, we chose to not include data derived from abstract books of international meetings.

## Differences between HCV-2 and HCV-3

The long-lasting practice to assess safety and efficacy of IFN-based therapies by cumulatively pooling data of HCV-2 and HCV-3 patients has been recently challenged by the Zeuzem study<sup>(19)</sup> which invariably demonstrated HCV-3 to be less sensitive to Peg-IFN alpha-2b (Peg $\alpha$ 2b) and RBV than HCV-2, suggesting that this difference was the consequence of higher rates of post-treatment relapse in the former group.

Following this study, information has gathered in the literature confirming these results. In fact, even in the absence of a randomized controlled study, HCV-3 patients have invariably achieved lower SVR rates when compared to HCV-2 patients in all studies (Table 1)<sup>(19-23)</sup>. Moreover, in these studies, steatosis and HCV viremia emerged as important predictors of treatment failure in HCV-3 but not in HCV-2 patients, suggesting that moderators of treatment outcome differ between these two genotypes.

**Table 1.** Differences in SVR rates between HCV genotype 2 and 3.

| Author                                 | No. | HCV-2 | No. | HCV-3 |
|----------------------------------------|-----|-------|-----|-------|
| Zeuzem <i>et al.</i> <sup>(19)</sup>   | 42  | 93%   | 183 | 79%   |
| Mangia <i>et al.</i> <sup>(20)</sup>   | 53  | 76%   | 17  | 76%   |
| Shiffman <i>et al.</i> <sup>(21)</sup> | 356 | 75%   | 369 | 66%   |
| Powis <i>et al.</i> <sup>(22)</sup>    | 67  | 81%   | 101 | 70%   |
| Ferenci <i>et al.</i> <sup>(23)</sup>  | 18  | 78%   | 123 | 67%   |

## Predictors of treatment outcome in HCV-3

The standard of care for patients with HCV-3 is a 24 week therapy regimen with a combination of Peg-IFN alpha-2a (Peg $\alpha$ 2a) or Peg-IFN alpha-2b plus RBV<sup>(24, 25)</sup>. This recommendation stems from the Hadziyannis<sup>(10)</sup> study and the Zeuzem<sup>(18)</sup> study respectively, which showed no benefit of a 48 week treatment schedule in terms of overall SVR rates. However, data on the efficacy of IFN-based therapies, as well as the identification of moderators of treatment outcome in HCV-3 patients, must be considered with caution since they are mostly

derived from further optimization or small cohort studies which might have been underpowered to detect significant differences in the subgroup analysis. Despite all these problems, it is noteworthy that bridging fibrosis/cirrhosis, high baseline viremia and lack of rapid virological response (RVR), i.e. HCV-RNA positivity at week 4 of treatment, have consistently emerged as predictors of treatment failure (Table 2) (19, 21, 22, 26, 27).

**Table 2.** Predictors of treatment failure in HCV-3 with corresponding SVR rates.

| Variable                           |            | SVR         | p        |
|------------------------------------|------------|-------------|----------|
| <b>Bridging fibrosis/cirrhosis</b> |            |             |          |
| Aghemo <i>et al.</i> (26)          | Yes vs. no | 35% vs. 84% | P=0.0005 |
| Powis <i>et al.</i> (22)           | Yes vs. no | 17% vs. 70% | P=0.004  |
| <b>High level of viremia</b>       |            |             |          |
| Zeuzem <i>et al.</i> (19)          | Yes vs. no | 70% vs. 86% | P=0.015  |
| Von Wagner <i>et al.</i> *(27)     | Yes vs. no | 67% vs. 84% | P=0.01   |
| <b>Steatosis &gt; 5%</b>           |            |             |          |
| Zeuzem <i>et al.</i> (19)          | Yes vs. no | NA°         | P=0.015  |
| <b>Absence of RVR</b>              |            |             |          |
| Zeuzem <i>et al.</i> (19)          | Yes vs. no | 69% vs. 85% | P=0.038  |
| Shiffman <i>et al.</i> *(21)       | Yes vs. no | 39% vs. 85% | P<0.0001 |

\* Standard duration group

° Not available

While the role of cirrhosis as a predictor of treatment failure in HCV-1 has been extensively demonstrated, its influence on SVR rates in HCV-3 patients has been only recently shown. In fact, the small number of HCV-3 cirrhotic patients enrolled in registration trials, coupled with the joint analysis of HCV-2 and 3 patients, prevented its emergence as a significant moderator of treatment outcome. Two recent papers from Italy and Canada, analyzing HCV-3 patients separately, have clearly demonstrated the dismal SVR rates achieved by Peg-IFN alpha-2b and Peg-IFN alpha-2a combo therapy in the presence of cirrhosis (35% and 17% respectively) (22, 26). While in the Italian paper this finding could be clearly attributed to the high rates of post-treatment relapse observed in cirrhotic patients (57% vs. 9%), this information was missing in the Canadian study (28).

Similarly, two studies showed that high baseline viremia determines lower SVR rates in HCV-3 patients (19, 27). However, a controversy exists on which cut-off value is more appropriate to define high viral load (>600.000 IU/mL vs. >800.000 IU/mL) and on which method is more reliable for HCV-RNA quantification, making this information

difficult to extrapolate into clinical practice.

The evidence on the negative predictive power of lack of RVR is more solid, since patients who are still HCV-RNA positive at week 4 have achieved SVR rates of between 39% and 59% in published studies (19, 21). These data, in fact, have been generated by multicenter studies enrolling a large number of patients and by definition are less likely to be influenced by enrolment biases and carry the strongest grade of evidence (29). Less clear is the influence of steatosis on treatment outcome, especially since HCV-3 has been shown to directly induce liver steatosis which regresses following viral eradication (30). While initial data suggested >5% steatosis to be associated with lower SVR rates, this finding could not be confirmed by other subsequent studies (31, 32), especially if non-invasive methods like fibroscan are used to define the degree of liver fibrosis (33).

The role of race has been recently investigated in an English study conducted among Caucasian and Asian HCV-3 infected patients. In this study, lower rates of SVR were observed in the latter group, suggesting that race may in fact play a role in determining treatment outcome. However, this study is far from being conclusive, mainly due to the small sample size and the possible confounding role of the higher prevalence of cirrhotics among the Asian subgroup of patients (34).

Taken altogether, these data clearly demonstrate the presence of a subgroup of HCV-3 patients that should not be considered as "easy to treat"; however, due to limitations either in the study design or in the sample size of the studies, these data unfortunately cannot be considered as conclusive evidence, and the interplay between these variables is still unknown.

### Abbreviated therapy for HCV-3 patients

The finding that maximal SVR rates could be achieved in HCV-3 patients with 24 weeks of treatment has prompted researchers to investigate even shorter durations of treatment for these patients. In fact, shorter treatment durations with retained efficacy would ameliorate the safety profile while reducing the costs of Peg-IFN plus RBV therapy. Following a pilot study by Dalgard *et al.* (35) published in 2004, 5 further studies with different designs investigated this issue (Table 3) (20, 21, 27, 36, 37).

What has emerged is that shorter treatment duration (12-16 weeks) should not be the standard of care for HCV-3 patients; since overall, they yield lower SVR rates than the conventional 24-week

**Table 3.** Studies investigating abbreviated therapies in patients infected with HCV-3.

| Study design                              | No. of patients | Therapy/Duration         |
|-------------------------------------------|-----------------|--------------------------|
| <b>Allocation by RVR</b>                  |                 |                          |
| mDalgard <i>et al.</i> <sup>(35)</sup>    | 98              | Peg 2b + Rbv w.b. 14w    |
| Mangia <i>et al.</i> <sup>(20)</sup>      | 53              | Peg 2b 1.0 + Rbv w.b 12w |
| <b>Randomization by RVR</b>               |                 |                          |
| Von Wagner <i>et al.</i> <sup>*(27)</sup> | 112             | Peg 2a + Rbv w.b 16w     |
| Dalgard <i>et al.</i> <sup>(36)</sup>     | 298             | Peg 2b + Rbv w.b 14w     |
| <b>Randomization at baseline</b>          |                 |                          |
| Shiffman <i>et al.</i> <sup>(21)</sup>    | 727             | Peg 2a + Rbv 800mg 16w   |
| Lagging <i>et al.</i> <sup>** (37)</sup>  | 276             | Peg 2a + Rbv 800mg 12w   |

\*Cut-off at 600 IU/ml;

\*\*Combined with HCV-2 pts  
w.b. = weight based

schedule, often as a consequence of higher relapse rates (21, 37).

The largest study conducted to investigate this issue is the ACCELERATE study, in which HCV-2 and HCV-3 patients were randomized at baseline to standard vs. abbreviated schedule. The "16 weeks" were overall less efficient than the "24 weeks" in terms of SVR rate, but this global result was mainly related to the disappointing SVR rates in genotype 2 patients treated with the abbreviated course. Even if the observed SVR rates in HCV-3 patients were similar between the 16 weeks schedule and the standard schedule (62% vs. 66%), the study reported significantly higher relapse rates in the former group in comparison with the latter group (31% vs. 22%,  $p < 0.01$ ) (21). Moreover, the relatively low dose of RBV used in the ACCELERATE study (800 mg/die) might have influenced the overall SVR rates, being ultimately responsible for the relatively low SVR rates achieved in the standard group. The choice of a fixed dose of 800 mg/die RBV coupled with Peg-IFN alfa-2a was a consequence of the Hadziyannis study (10) which failed to demonstrate any benefit in using higher RBV doses in HCV-3 and 2 patients. However, RBV has been used at a weight-based dosing in most abbreviated therapy studies (20, 27, 36) and therefore the optimal dose of RBV required in abbreviated courses is still unknown.

Another important finding derived from all studies published so far is that patients lacking RVR cannot benefit from abbreviated therapies, as SVR rates do not top 41% in this subgroup of patients.

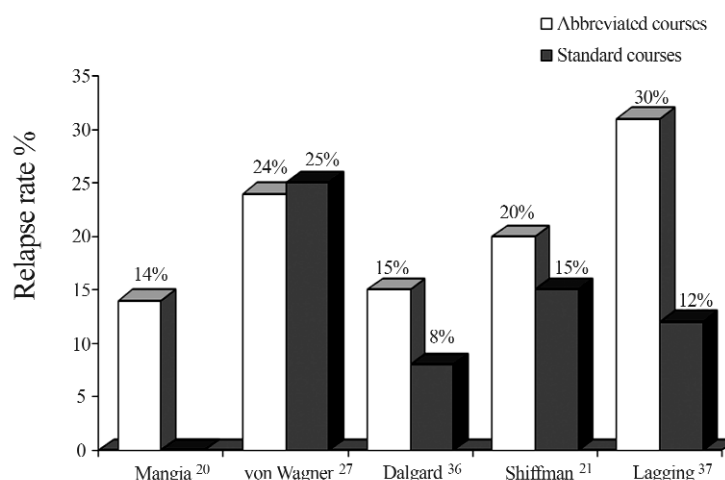
When analyzing only patients with an

RVR, the abbreviated course yielded similar SVR rates compared to the standard duration group, suggesting that HCV-RNA negativity at week 4 is essential to shorten the therapy (Table 4).

**Table 4.** SVR rates in HCV-3 patients achieving an RVR.

| Reference                                | Abbreviated Therapy | Standard Therapy | P     |
|------------------------------------------|---------------------|------------------|-------|
| Dalgard <i>et al.</i> <sup>(35)</sup>    | 89%                 | -                | -     |
| Mangia <i>et al.</i> <sup>(20)</sup>     | 77%                 | 100%             | 0.2   |
| Von Wagner <i>et al.</i> <sup>(27)</sup> | 76%                 | 75%              | 0.9   |
| Shiffman <i>et al.</i> <sup>(21)</sup>   | 80%                 | 85%              | 0.2   |
| Dalgard <i>et al.</i> <sup>(36)</sup>    | 84%                 | 92%              | 0.1   |
| Lagging <i>et al.</i> <sup>(37)</sup>    | 71%                 | 91%              | 0.001 |

However, three important issues should not be overlooked when analyzing this finding. First of all, the only study designed to demonstrate the non-inferiority of a 14-week course versus the standard 24-week treatment schedule, although reporting high SVR rates in both groups (84% vs. 92%, respectively), failed to achieve its endpoint (37). Secondly, the abbreviated schedules were associated with higher relapse rates in all studies (Fig. 1). Thirdly and most important of all, two studies demonstrated that bridging fibrosis/cirrhosis and high baseline viremia were predictors of treatment failure even in this subset of highly responsive patients (22, 26). Altogether, in our opinion, these data suggest that while RVR is essential to consider shorter treatment courses, it is in no way sufficient since in the presence of known predictors of treatment outcome, such as cirrhosis and/or high baseline viremia, the abbreviated treatment

**Figure 1.** Relapse rates in standard and abbreviated courses of therapy in HCV-3 patients achieving an RVR.

schedules achieve significantly lower SVR rates when compared to the standard duration therapy. In our opinion, before shorter treatment durations become universally acceptable for patients with an RVR, further randomized studies with attention to the aforementioned baseline moderators of treatment outcome are mandatory.

### Extending treatment duration in "hard to treat" patients

While the relevance of identifying predictors of treatment failure in HCV-3 patients should not be discarded, unfortunately we still have no answer on how to improve SVR rates in these "hard to treat" patients. Since post treatment relapse more than primary non response is ultimately responsible for the high rates of treatment failure observed in cirrhotics and in those with high baseline viremia (18, 26, 38, 39), the use of triple therapy with protease inhibitors, which have shown to achieve potent and rapid viral suppression in HCV-1 patients (40-42), might not be the answer in HCV-3 infected patients. However, to answer this question, Phase II studies have been designed and are currently ongoing in Europe. In theory, as a means to reduce post treatment relapse rates, treatment extension to 48 weeks might be advisable as recommended in HCV-3/HIV co-infected patients (43). Moreover, extended treatment schedules, such as the 72 week-therapy course studied in HCV-1 slow responders, a subgroup of patients characterized by high post treatment relapse rates, have shown to significantly improve SVR mainly through a reduction in relapse rates (44-46). However, to our knowledge, no data has been published on this strategy in HCV-3; therefore, in the absence of a randomized study, this approach should not be employed in clinical practice.

### Conclusions

This review challenges the commonly held opinion that HCV-3 infection is an "easy to treat" genotype, as demonstrated by the less than optimal SVR rates in a subgroup of patients who can be identified by the presence of bridging fibrosis/cirrhosis, high baseline viremia and lack of an RVR. The influence of liver steatosis, on the contrary, still needs further confirmation. To date, we have no data on how to improve treatment efficacy in this subgroup of patients; in fact, while treatment extension to 48 weeks might be of benefit,

it cannot be formally recommended in clinical practice.

Abbreviated courses of Peg-IFN/RBV therapy (12-16 weeks) should be proposed only to patients with an RVR as they yield significantly lower SVR rates in patients who are still HCV-RNA positive at week 4. Still, the patient should be informed that a higher risk of post-treatment relapse is to be expected. Moreover, we think that before universal acceptance of abbreviated therapies as the standard of care for HCV-3 patients with an RVR, further data is needed to explore the interplay between RVR, degree of fibrosis, levels of baseline HCV-RNA or other relatively unknown predictors such as BMI to assess the real efficacy of this strategy in these patients.

### References

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science*. 1989;244(4902):359-62.
2. Alter HJ, Purcell RH, Shih JW, *et al*. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. *N Engl J Med*. 1989;321(22):1494-500.
3. Saito I, Miyamura T, Ohbayashi A, *et al*. Hepatitis C virus infection is associated with the development of hepatocellular carcinoma. *Proc Natl Acad Sci U S A*. 1990;87(17):6547-9.
4. Lagging LM, Westin J, Svensson E, *et al*. Progression of fibrosis in untreated patients with hepatitis C virus infection. *Liver*. 2002;22(2):136-44.
5. Bruno S, Stroffolini T, Colombo M, *et al*. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology*. 2007;45(3):579-87.
6. Hoofnagle JH, Seeff LB. Peginterferon and ribavirin for chronic hepatitis C. *N Engl J Med*. 2006;355(23):2444-51.
7. Pawlotsky JM. Therapy of hepatitis C: from empiricism to eradication. *Hepatology*. 2006;43(2 Suppl 1):S207-20.
8. Manns MP, McHutchison JG, Gordon SC, *et al*. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001;358(9286):958-65.
9. Fried MW, Shiffman ML, Reddy KR, *et al*. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002;347(13):975-82.
10. Hadziyannis SJ, Sette H, Jr., Morgan TR, *et al*. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med*. 2004;140(5):346-55.
11. Simmonds P. Viral heterogeneity of the hepatitis C virus. *J Hepatol*. 1999;31 Suppl 1:54-60.
12. Bortolotti F, Iorio R, Resti M, *et al*. Epidemiological profile of 806 Italian children with hepatitis C virus infection over a 15-year period. *J Hepatol*. 2007;46(5):783-90.
13. Kabir A, Alavian SM, Keyvani H. Distribution of hepatitis C virus genotypes in patients infected by different sources

- and its correlation with clinical and virological parameters: a preliminary study. *Comp Hepatol*. 2006;**5**:4.
14. Payan C, Roudot-Thoraval F, Marcellin P, et al. Changing of hepatitis C virus genotype patterns in France at the beginning of the third millenium: The GEMHEP GenoCII Study. *J Viral Hepat*. 2005;**12**(4):405-13.
  15. Pybus OG, Cochrane A, Holmes EC, Simmonds P. The hepatitis C virus epidemic among injecting drug users. *Infect Genet Evol*. 2005;**5**(2):131-9.
  16. Esteban JI, Sauleda S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. *J Hepatol*. 2008;**48**(1):148-62.
  17. Neumann AU, Lam NP, Dahari H, et al. Differences in viral dynamics between genotypes 1 and 2 of hepatitis C virus. *J Infect Dis*. 2000;**182**(1):28-35.
  18. Zeuzem S, Herrmann E, Lee JH, et al. Viral kinetics in patients with chronic hepatitis C treated with standard or peginterferon alpha2a. *Gastroenterology*. 2001;**120**(6):1438-47.
  19. Zeuzem S, Hultcrantz R, Bourliere M, et al. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J Hepatol*. 2004;**40**(6):993-9.
  20. Mangia A, Santoro R, Minerva N, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N Engl J Med*. 2005;**352**(25):2609-17.
  21. Shiffman ML, Suter F, Bacon BR, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med*. 2007;**357**(2):124-34.
  22. Powis J, Peltekian KM, Lee SS, et al. Exploring differences in response to treatment with peginterferon alpha 2a (40kD) and ribavirin in chronic hepatitis C between genotypes 2 and 3. *J Viral Hepat*. 2008;**15**(1):52-7.
  23. Ferenci P, Brunner H, Laferl H, et al. A randomized, prospective trial of ribavirin 400 mg/day versus 800 mg/day in combination with peginterferon alfa-2a in hepatitis C virus genotypes 2 and 3. *Hepatology*. 2008;**47**(6):1816-23.
  24. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. *Hepatology*. 2004;**39**(4):1147-71.
  25. Dienstag JL, McHutchison JG. American Gastroenterological Association medical position statement on the management of hepatitis C. *Gastroenterology*. 2006;**130**(1):225-30.
  26. Aghemo A, Rumi MG, Soffredini R, et al. Impaired response to interferon-alpha2b plus ribavirin in cirrhotic patients with genotype 3a hepatitis C virus infection. *Antivir Ther*. 2006;**11**(6):797-802.
  27. von Wagner M, Huber M, Berg T, et al. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology*. 2005;**129**(2):522-7.
  28. Aghemo A, Rumi MG, Colombo M. Is a 24 week treatment schedule with PegInterferon and Ribavirin too short for HCV genotype 3 cirrhotics? *J Viral Hepat*. 2008;**15**(6):471.
  29. Vandenbroucke JP. When are observational studies as credible as randomised trials? *Lancet*. 2004;**363**(9422):1728-31.
  30. Poynard T, Ratziu V, McHutchison J, et al. Effect of treatment with peginterferon or interferon alfa-2b and ribavirin on steatosis in patients infected with hepatitis C. *Hepatology*. 2003;**38**(1):75-85.
  31. Westin J, Lagging M, Dhillon AP, et al. Impact of hepatic steatosis on viral kinetics and treatment outcome during antiviral treatment of chronic HCV infection. *J Viral Hepat*. 2007;**14**(1):29-35.
  32. Moucari R, Asselah T, Cazals-Hatem D, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. *Gastroenterology*. 2008;**134**(2):416-23.
  33. Fraquelli M, Rigamonti C, Casazza G, et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. *Gut*. 2007;**56**(7):968-73.
  34. Freshwater DA, O'Donnell K, Mutimer DJ. Inferior response of Asian vs non-Asian hepatitis C genotype 3 infection to combination antiviral therapy. *J Viral Hepat*. 2008;**15**(2):115-9.
  35. Dalgard O, Bjoro K, Hellum KB, et al. Treatment with pegylated interferon and ribavirin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. *Hepatology*. 2004;**40**(6):1260-5.
  36. Dalgard O, Bjoro K, Ring-Larsen H, et al. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology*. 2008;**47**(1):35-42.
  37. Lagging M, Langeland N, Pedersen C, et al. Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. *Hepatology*. 2008;**47**(6):1837-45.
  38. Aghemo A, Rumi MG, Monico S, Prati GM, Ronchi G, Colombo M. Genotype dependent pattern of Peginterferon alfa-2B/Ribavirin treatment failure in hepatitis C virus infected patients with cirrhosis: A single centre study of 471 naïve patients. *Digestive and Liver Disease*. 2008;**40**(5):2-3.
  39. Mangia A, Minerva N, Bacca D, et al. 8 Factors Predictive of Relapse in Genotype 2 and 3 Pts Treated for 12 Weeks with Peg-IFN Alfa 2b and Weight Based Ribavirin Combination. *Journal of Hepatology*. 2008;**48**(2):6.
  40. Lawitz E, Rodriguez-Torres M, Muir AJ, et al. Antiviral effects and safety of telaprevir, peginterferon alfa-2a, and ribavirin for 28 days in hepatitis C patients. *J Hepatol*. 2008;**49**(2):163-9.
  41. McHutchison J, Everson G, Gordon S. PROVE1: results from phase II study of Telaprevir with Peg-interferon alfa-2a ribavirin in treatment naïve subjects with hepatitis C. *J Hepatol*. 2008;**48**(S2):S4.
  42. Dusheiko GM, Hezode C, Pol S. Treatment of chronic hepatitis C with telaprevir (TVR) in combination with peginterferon-alfa-2a with or without ribavirin: further interim analysis results of the PROVE2 study. *J Hepatol*. 2008;**48**(Suppl 2):S26.
  43. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med*. 2004;**351**(5):438-50.
  44. Berg T, von Wagner M, Nasser S, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology*. 2006;**130**(4):1086-97.
  45. Sanchez-Tapias JM, Diago M, Escartin P, et al. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology*. 2006;**131**(2):451-60.
  46. Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. *Hepatology*. 2007;**46**(6):1688-94.