Optimal Duration of Pegylated Interferon Plus Ribavirin Therapy for Chronic Hepatitis C Genotype 3 Patients who do not Achieve Rapid Virological Response

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Background/Objectives: Chronic hepatitis C (CHC) genotype-3 (G-3) patients treated with standard 24-week pegylated interferon plus ribavirin (PEG-RBV) therapy achieve sustained virological response (SVR) rate of 69–82%. Patients who do not achieve rapid virological response (RVR) have lower SVR rate. Data regarding optimal management of this subgroup is scarce. We aimed to determine the most appropriate treatment duration in CHC G-3 patients who do not achieve RVR. **Methods:** Treatment naïve CHC G-3 patients treated with PEG-RBV therapy were included in this retrospective analysis. Patients with cirrhosis were excluded. RVR was assessed in all patients beyond the year 2007. RVR non-achievers were advised extended treatment beyond 24 weeks. **Results:** Of the total 685 patients started on treatment, 646 completed treatment (mean age 39.1 ± 12 years, 68.3% males). In the pre-‘RVR assessment’ period (2004–2006), SVR with standard 24 week therapy was 72.3% (112/155). In post-‘RVR assessment’ period (2007–2013), 75.8% (402/530) patients achieved RVR; and 91.5% (368/402) of these achieved SVR with standard 24 weeks therapy. Among RVR non-achievers ($n = 128$), 51 patients opted for extended 36 week therapy, 12 for 48 week therapy, while 65 stopped therapy at 24 weeks. Choice of treatment duration was dependent entirely on the affordability of the patient. SVR with extended therapy (36/48 weeks) was significantly higher than standard 24 week therapy in RVR non-achievers (82.5% vs. 52.3%; $P = 0.003$). However, SVR rate in 36 week group was not significantly different from 48 week group (84.3% vs. 75%; $P = 0.425$). On multivariate analysis, duration of treatment (36/48 week vs. 24 week; $P < 0.001$) was significantly associated with SVR. **Conclusions:** SVR rates in CHC G-3 patients treated with PEG-RBV in northern India were comparable to western data. Standard 24 week therapy is adequate for RVR-achievers. However, in RVR non-achievers, extended 36 week therapy significantly improves SVR, while further extension to 48 week does not provide any additional advantage. (J CLIN EXP HEPATOL 2015;5:2–7)

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide.¹ Chronic hepatitis C (CHC) has been conventionally treated with combination of pegylated interferon-alpha and ribavirin (PEG-RBV) therapy since many years.^{1,2} Although newer therapeutic options have been recently

approved for the treatment of CHC,^{3,4} their use in the developing countries is limited due to high cost and non-availability. Various host and virological factors are known to affect the response to treatment, of which HCV genotype and treatment duration are important factors affecting sustained virologic response (SVR).¹ Genotype 3 (G-3) is the most common genotype in South-east Asia.^{5,6} The recommended duration of PEG-RBV therapy for CHC treatment-naïve G-3 patients is for 24 weeks, which provides SVR rates of 69–82%.^{1,2} Hadzyannis et al compared the efficacy of 48 weeks versus 24 weeks PEG-RBV therapy in CHC G-3 patients and reported no significant difference in overall SVR rates in the 2 arms.⁷ However, in their study, analysis was done based on early virological response (EVR) and SVR, as the concept of rapid virological response (RVR) had not evolved by that time. After the concept of RVR evolved, it was noted that G-3 patients who do not achieve RVR have significantly lower (36–62%) SVR rates with the standard 24 week PEG-RBV therapy,^{8–12} suggesting that extension of therapy is

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Abbreviations: HCV: Hepatitis C virus; CHC: Chronic hepatitis C; SVR: sustained virologic response; EVR: early virological response; HIV: Human Immunodeficiency virus; HBV: hepatitis B virus; PTI: prothrombin time index; ALT: alanine aminotransferase; BMI: Body mass index; cEVR: Complete EVR

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required in this subgroup of patients. However, the appropriate duration and the benefit of extended response guided PEG-RBV therapy for genotype 3 patients who do not achieve RVR has not been addressed adequately in literature.¹

In the present study, we report the SVR rates in a large cohort of CHC G-3 patients treated in a real-life setting, and study the factors affecting SVR. In addition, we evaluated the usefulness of extension of PEG-RBV therapy beyond the standard 24 week duration in CHC G-3 patients who do not achieve RVR, with the aim of determining the most appropriate duration of PEG-RBV treatment in this sub-group of patients.

MATERIALS AND METHODS

This retrospective analysis included all treatment naïve CHC G3 patients treated in the gastroenterology outpatient department of a tertiary care institute in northern India between January 2004 and December 2013. Patients who had evidence of cirrhosis, co-infections with hepatitis B virus (HBV) or Human Immunodeficiency virus (HIV), or who had a history of previous antiviral or immunomodulatory therapy were also treated at our institute as per the indications, but were not included in this study. Patients who had contraindications for anti-viral therapy i.e. decompensated liver disease, active alcohol or drug abuse, major neuro-psychiatric illness, uncontrolled thyroid disorder or uncontrolled diabetes, autoimmune diseases, advanced cardio-pulmonary disease, renal failure, hemoglobin <12 g/dl (females) or <13 g/dl (males), platelet count <90,000/mm³ or neutrophil count <1500/mm³ were not offered anti-viral treatment.

Detailed history taking and clinical examination were done. Baseline laboratory work-up included hemogram, liver and renal function tests, thyroid function tests, prothrombin time index (PTI), fasting blood sugar, α -feto protein and ultrasound abdomen. Cirrhosis was diagnosed on the basis of clinical, laboratory, radiological, endoscopic and/or histological criteria (where available). Elastography measurement was done in all patients beyond the year 2009. Increased alanine aminotransferase (ALT) was defined as ALT levels >40 IU/L. All the patients were tested for HBV and HIV co-infections. Work-up for autoimmune and metabolic diseases was done, where indicated. Anti-HCV antibody positivity was confirmed by ELISA (ELISCAN HCV; RFCL limited, Dehradun, India). HCV Ribo-Nucleic Acid (RNA) was quantified by real time polymerase chain reaction technology (COBAS Taqman HCV TEST 2.0; Roche Diagnostics Corporation, Indianapolis, IN, USA). High viral load was defined as HCV RNA >4,00,000 IU/ml. HCV Genotype was also determined in all patients.

Patients were treated with or PEG-IFN α 2b (PEG-Intron, Schering Corp, Kenilworth, NJ, USA) (1.5 μ g/kg per week)

or PEG-IFN α 2a (Pegasys, Hoffmann-LaRoche) (180 μ g per week) subcutaneously plus ribavirin 800–1200 mg/day orally, according to body weight (<65 kg, 800 mg/day; 65–85 kg, 1000 mg/day; >85 kg, 1200 mg/day).

At the initiation of the therapy, patients were offered standard PEG-RBV therapy of 24 weeks duration. Testing for HCV RNA at 4 weeks for RVR (defined as undetectable HCV RNA) was done beyond the year 2007. During the pre-‘RVR assessment’ period (year 2004–2006), all patients received standard therapy for 24 weeks. In the post-‘RVR assessment’ period (year 2007–2013), patients who achieved RVR received standard 24 weeks therapy. Patients who did not achieve RVR were advised extension of therapy to 48 weeks. However, those who were not willing to double the duration of therapy to 48 weeks were advised to receive at least 36 week therapy. Patients who did not agree for extension of therapy due to either financial reasons or fear of adverse events, and stopped treatment at 24 weeks only were also included in analysis. The choice of duration of therapy (i.e. 24, 36 or 48 weeks) was dependent mainly on the affordability of the patient.

All patients were then followed up for additional 24 weeks after treatment to assess SVR. Treatment was considered to be ‘complete’ if the patient received >80% dose of both the treatment drugs for >80% of the recommended duration. Dose adjustments for adverse effects were made according to standard protocols. Antidepressants and growth factors (erythropoietin or granulocyte colony stimulating factor) were used based on clinical condition of the patient or laboratory abnormalities.^{13,14} Treatment was withdrawn prematurely by the treating physicians in case of non-response (HCV RNA positivity persisting after 24 weeks of therapy or viral load not decreasing by at least 2 log IU/ml after 12 weeks of therapy).

Patients were evaluated as outpatients for safety and efficacy at regular intervals. Routine hematology was done at 2 and 4 weeks, then every 4 weeks and whenever required. Liver biochemistry was monitored every 4 weeks and thyroid-stimulating hormone levels every 12 weeks during treatment. HCV RNA was repeated at 4 weeks (beyond the year 2007) for assessment of RVR, at 12 weeks (in all patients) for detecting EVR. Complete EVR (cEVR) was defined as HCV RNA negativity at 12 weeks and partial EVR (pEVR) as HCV RNA reduction by >2 log at 12 weeks but not becoming negative. HCV RNA was repeated at 24 weeks while on treatment for all patients (in addition at 36 and 48 weeks for patients receiving extended duration therapy). HCV RNA at 24 weeks post-treatment was done for detecting SVR (defined as undetectable HCV RNA).

Study Outcome Measures and Endpoints

The primary outcome measure was the proportion of patients achieving SVR. The secondary outcome measures were the proportion of patients who achieved RVR and EVR.

The primary endpoint of the study was completion of 24 weeks of follow up after completion of full recommended therapy. Secondary end-points were premature withdrawal of treatment in non-responders or in patients with severe side effects, or patient being lost to follow up.

Safety and tolerability were assessed by monitoring adverse events (influenza-like symptoms, gastrointestinal, respiratory, dermatological, neuropsychiatric side effects etc.) and laboratory abnormalities (anemia, leucopenia/neutropenia, thrombocytopenia) when they were reported during the treatment.

Statistical Analysis

All data were analyzed using SPSS v. 14.0 software package. Continuous data were expressed as means $\pm$ SD. Categorical data were expressed as number/proportion of subjects with a specific feature. Chi-square test was used to compare categorical data. Analysis was performed on an 'intention-to-treat' basis. Multivariate logistic regression was performed to identify independent predictors of RVR and SVR, considering them as the dependent variables. A two-tailed *p* value of less than 0.05 was required for statistical significance.

RESULTS

A total of 685 patients with chronic HCV genotype 3 infection were treated with PEG-RBV combination therapy at our institute over a period of 10 years. Out of these, 646 (94.3%) patients completed minimum 24 weeks therapy and 6 months post-treatment follow-up. The remaining 39 (5.7%) patients did not complete the treatment and/or follow-up. Various reasons for non-completion of therapy were patients lost to follow up (3.2%, *n* = 22), stoppage of therapy by the treating physician due to non-tolerability of treatment (1.9%; *n* = 13), discontinuation of treatment

by physician due to non-response (0.3%, *n* = 2) and deaths due to non-hepatic causes (0.3%, *n* = 2).

Baseline characteristics of all the patients are shown in Table 1. The mean age was 39.1 ± 12 years, and 68.3% (*n* = 468) were males. The mean BMI was 24.2 ± 4.1 and mean ALT was 107.9 ± 98.6 IU/L. HCV viral load $>4,00,000$ IU/ml was present in 47.3% (*n* = 324). Co-morbidities were present in 16.5% (*n* = 113) [diabetes mellitus 9.9% (*n* = 68), cardio-vascular disease 2.3% (*n* = 16), neurological diseases 1.7% (*n* = 12), respiratory diseases 1.6% (*n* = 11), renal disorders 0.4% (*n* = 3), others 0.4% (*n* = 3)]. Past history of significant alcohol use was present in 10.8% (*n* = 74).

Flow of patients in the study and SVR rates in various sub-groups is shown in Figure 1. The overall SVR rate in all the treated CHC G-3 patients was 82.6% (566/685) (intention-to-treat analysis). In the pre-'RVR assessment' period (year 2004–2006), the SVR rate in CHC patients treated with standard therapy for 24 weeks was 72.3% (112/155). In the post-'RVR assessment' period (year 2007–2013), 75.8% (402/530) patients achieved RVR. The SVR rate among patients who achieved RVR and received standard 24 weeks therapy was 91.5% (368/402). All the RVR non-achievers (*n* = 128) achieved EVR at 12 weeks. The RVR non-achievers were advised extended duration therapy beyond 24 weeks. Out of these, 51 patients agreed for 36 week duration therapy, 12 patients agreed for 48 week therapy, while 65 patients stopped therapy at 24 weeks only. Baseline characteristics in these three groups were similar (Table 1). RVR non-achievers who received standard 24 week therapy had a significantly lower SVR rate (52.3%; 34/65) compared to those who received extended therapy (82.5%; 52/63) (*P* = 0.003). However, the SVR rates in the 36 week duration group was not significantly different from that in the 48 week duration group [84.3% (43/51) vs. 75% (9/12) respectively; *P* = 0.425].

Table 1 Baseline Characteristics of Chronic Hepatitis C Genotype 3 Patients.

Parameter	All patients (<i>n</i> = 685)	Treatment groups of non-RVR patients ^a		
		24 week therapy group (<i>n</i> = 65)	36 week therapy group (<i>n</i> = 51)	48 week therapy group (<i>n</i> = 12)
Age (years)	39.1 ± 12	42.6 ± 12.8	49.1 ± 9.4	49.4 ± 8.8
Males	68.3 (468)	58.5 (38)	64.7 (33)	58.3 (7)
BMI (kg/m ²)	24.2 ± 4.1	23.6 ± 4.4	24.4 ± 2.8	26.7 ± 5.5
ALT (IU/L)	107.9 ± 98.6 IU/L	77.8 ± 59.8	91.5 ± 58.6	91 ± 53.1
HCV RNA $>4,00,000$ IU/ml	47.3 (324)	60 (39)	56.8 (29)	58.3 (7)
Presence of any co-morbid condition	16.5 (113)	18.5 (12)	19.6 (10)	25 (3)
Presence of Diabetes Mellitus	9.9 (68)	12.3 (8)	13.7 (7)	25 (3)
Past history of alcohol use	10.8 (74)	10.7 (7)	13.7 (7)	8.3 (1)

Data are expressed as mean $\pm$ SD or percentage (number).

ALT, Alanine transaminase; BMI, Body mass index; HCV RNA, Hepatitis C virus ribonucleic acid; RVR, Rapid virological response.

^a*P* values for all comparison of all parameters among the three treatment groups were non-significant (>0.05).

Figure 1 Flow of patients and sustained virological response (SVR) rates in the study. cEVR, complete early virological response; RVR, rapid virological response.

Treatment related adverse events were noted in 75.3% (n = 516) patients. The adverse effect profile was not significantly different between the three groups. The most common adverse events were—fatigue (75.3%), pyrexia (70.9%), anorexia (60.8%), alopecia (42.2%), anemia (hemoglobin <10 g/dl) (22.7%) and depression (18.4%). Ribavirin dose modification was required in 23.7% (163/685) patients and PEG-IFN dose modification in 10.8% (74/685) patients. Erythropoietin supplementation was required in 22.1% (n = 152), GM-CSF in 9.2% (n = 63) and blood transfusion in 7.2% (n = 49) patients.

Factors Associated with RVR and SVR

Multiple logistic regression analysis was performed to find the factors associated with RVR (in all patients) and SVR (in RVR non-achievers). Various factors studied for association with RVR were—age, sex, BMI, past alcohol use, co-morbidities, diabetes, baseline ALT, baseline viral load, ribavirin dose and PEG-IFN dose. None of these factors was found to be associated with RVR on univariate and multivariate analysis. Factors studied for association with SVR (in RVR non-achievers) are shown in Table 2. On univariate analysis, factors significantly associated with SVR were—age <40 years ($P = 0.02$), absence of diabetes mellitus ($P = 0.03$), no reduction in PEG-IFN dose ($P = 0.041$) and longer duration of treatment (36/48 week vs. 24 week; $P < 0.001$) was found to be significantly associated with SVR.

DISCUSSION

The present study evaluated the efficacy and safety of PEG-RBV combination therapy in a large cohort of CHC G-3 patients treated in a ‘real-life’ setting in northern India. In addition, we evaluated the significance of extension of ther-

Table 2 Univariate and Multivariate Logistic Regression Analysis of Various Baseline and Treatment Factors Associated with Sustained Virological Response in RVR Non-achievers (n = 128).

Variables	Univariate analysis	Multivariate analysis	
	P value	O.R. (95% C.I.)	P value
Baseline factors			
Age (≤ 40 years vs. > 40 years)	0.02	1.49 (0.84–2.58)	0.26
Sex (female vs. male)	0.36		
BMI (≤ 25 vs. > 25 kg/m ²)	0.47		
ALT (> 40 IU/L vs. ≤ 40 IU/L)	0.64		
HCV viral load ($\leq 4,00,000$ IU/ml vs. $> 4,00,000$ IU/ml)	0.81		
Past alcohol use (absent vs. present)	0.61		
Co-morbid conditions (absent vs. present)	0.37		
Diabetes mellitus (absent vs. present)	0.03	0.34 (0.15–0.63)	0.81
Treatment factors			
Ribavirin dose (no reduction vs. reduction)	0.44		
Pegylated Interferon dose (no reduction vs. reduction)	0.041	1.64 (0.83–3.28)	0.15
Duration of treatment (36/48 week vs. 24 week)	< 0.001	8.63 (3.76–17.14)	< 0.001

ALT, Alanine transaminase; BMI, Body mass index; HCV Hepatitis C virus; RVR, rapid virological response; SVR, sustained virological response.

apy beyond 24 weeks in patients who do not achieve RVR. The main findings of our study are—a good overall SVR rate of 82.6% in CHC G-3 treatment naïve patients with PEG-RBV therapy; significantly better SVR rate with extension of therapy to 36 weeks in patients who did not achieve RVR; and no additional benefit of extending the therapy to 48 weeks in RVR non-achievers.

HCV genotype 3 is the most prevalent genotype in the Indian subcontinent,^{5,6} with a prevalence rate of 65–75% compared to about 20–50% in western population. The overall SVR rate among G-3 patients reported in our study (82.6%) is comparable to the SVR rates of 76–84% reported in most of the studies from the western world.^{7,15–17} However, few studies^{18,19} have reported lower SVR rates (66–68%) in genotype 3 patients. Difference in the patient population and dosage of ribavirin might be responsible for this variation.

RVR is an important predictor of SVR. In the present study, 72.3% patients achieved RVR. Previous studies have reported an RVR rate of 62–68% in genotype 2/3 infected patients,^{1,20} while a higher (71–93%) RVR rate has been reported in studies using weight based ribavirin.²⁰ With a standard 24 week course of therapy, SVR rate of 80–91% has been reported in RVR achievers whereas RVR non-achievers have 36–62% SVR rate.^{8–12,20} Similar results were noted in the present study where the SVR rates with standard 24 week therapy in RVR achievers and RVR non-achievers were 91.5% and 52.3% respectively. These data emphasize the need for extended therapy in CHC G3 patients who do not achieve RVR. However, there is scarcity of data on the benefit of extended duration therapy in G3 RVR non-achievers. The HCV treatment guidelines by AASLD do not recommend extension of therapy due to lack of published data,²¹ while the EASL guidelines state that such patients ‘can be’ treated for 48 weeks. A study by Willems et al²² (published in abstract form

only) reported 76% SVR rate with 48 week PEG-RBV therapy compared to 65% with 24 week therapy in G2/3 patients who did not achieve RVR. Another recently published abstract²³ reported similar benefit of 48 week therapy in CHC G2/3 RVR non-achievers. The logic of extending the therapy directly from 24 weeks to 48 weeks is not clear, but is based on the principle of consolidation phase after viral eradication. It is already known that the SVR rate inversely correlates with the time on treatment that is necessary to clear HCV RNA from serum.²⁴ Results of the present study clearly show that in G3 RVR non-achievers, 36 week therapy is superior to 24 week therapy but extension of therapy to 48 weeks offers no additional advantage. Thus, CHC G3 patients who do not achieve RVR (but achieve EVR) definitely need extension of therapy, but it may be sufficient to extend the PEG-RBV therapy to 36 weeks rather than 48 weeks. This would lead to a 50% reduction in the additional cost of treatment, and lesser morbidity for the patients.

We propose a new response guided strategy for PEG-RBV therapy in CHC G3 patients (Figure 2). Patients who achieve RVR should receive standard 24 week therapy. However, in a selected sub-group of these RVR-achievers who have low viral load (<4,00,000 IU/ml), therapy may be shortened to 12–16 weeks, as recommended by most of the guidelines.¹ In RVR non-achievers (but who achieve EVR), 36 weeks therapy may be sufficient, while those who achieve partial EVR, 48 week therapy may be required. Therapy should be stopped at 12 weeks in patients who do not achieve >2 log reduction in viral load at 12 weeks.¹

Our study has few limitations. First, the distribution of RVR non-achievers into 24 weeks, 36 weeks or 48 week therapy groups was based on patient preferences, and not on randomization protocol. However, as the patient characteristics in the three groups were similar, this is unlikely to affect the results. Secondly, the number of patients

Figure 2 Proposed algorithm for response guided Pegylated Interferon plus ribavirin therapy for chronic hepatitis C genotype 3 patients. cEVR, complete early virological response; pEVR, partial early virological response; RVR, rapid virological response.

in the 48 week treatment arm was small, which did not allow for a robust statistical analysis. The primary reason for this is that CHC G3 patients, who start treatment with the intent of ending it at 24 weeks, do not agree for doubling the therapy to 48 weeks because of incremental costs and side-effects. However, despite the low number of patients in the 48 week treatment arm, the SVR rate in this arm in our study is similar to that reported earlier. Thus, it can be used for comparison with the 36 week treatment arm. Moreover, with the possibility of new interferon free regimens likely to become available in very near future, it may not be possible to plan randomized trials with PEG-RBV therapy based protocols. Thirdly, the IL28B data was available for few patients only, so its effect on SVR could not be analyzed. However, since the impact of IL28B for G3 patients is not well established as it is for G1 patients, it might not be an important factor for this study.

To conclude, the SVR rates in CHC G-3 patients in northern India were comparable to western data. For CHC G-3 patients who achieve RVR, 24 week therapy is adequate. However, those who fail to achieve RVR (but achieve EVR), extension of therapy to 36 weeks is required as it results in significantly higher SVR rates. Further extension of therapy to 48 weeks does not provide any additional advantage.

CONFLICTS OF INTEREST

All authors have none to declare.

REFERENCES

- European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. *J Hepatol*. 2011;55:245–264.
- Sood A, Midha V, Goyal O, Hissar S, Sharma SK, Khanna P. Treatment of chronic hepatitis C with pegylated interferon plus ribavirin in treatment-naïve 'real-life' patients in India. *Indian J Gastroenterol*. 2014;33:343–349.
- European Association for Study of Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol*. 2014;60:392–420.
- Feeney ER, Chung RT. Antiviral treatment of hepatitis C. *BMJ*. 2014;349:g3308.
- Hissar SS, Goyal A, Kumar M, et al. Hepatitis C virus genotype 3 predominates in north and central India and is associated with significant histopathologic liver disease. *J Med Virol*. 2006;78:452–458.
- Sood A, Midha V, Goyal O. Genotypic distribution and associated disease pattern of hepatitis C virus in northern India. *J Gastrointest Infect*. 2014;4:40–43.
- Hadziyannis SJ, Sette H, Morgan TR. Peginterferon alfa-2a (40 kilodaltons) and ribavirin combination therapy in chronic hepatitis C: randomized study of the effect of treatment duration and ribavirin dose. *Ann Intern Med*. 2004;140:346–355.
- 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;40:1260–1265.
- 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;352:2609–2617.
- von Wagner M, Huber M, Berg T, et al. Peginterferon-alfa-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology*. 2005;129:522–527.
- 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;47:35–42.
- 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;47:1837–1845.
- Curry MP, Afdhal NH. Use of growth factors with antiviral therapy for chronic hepatitis C. *Clin Liver Dis*. 2005;9:439–451.
- Aspinall RJ, Pockros PJ. Review article: the management of side effects during therapy for hepatitis C. *Aliment Pharmacol Ther*. 2004;20:917–929.
- Manns M, McHutchinson J, Gordon SC, et al. Peg-interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001;358:958–965.
- Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis virus infection. *N Eng J Med*. 2002;347:975–982.
- Borroni G, Andreoletti M, Casiraghi MA, et al. Effectiveness of pegylated interferon/ribavirin combination in 'real world' patients with chronic hepatitis C virus infection. *Aliment Pharmacol Ther*. 2008;27:790–797.
- Pariente A, Lahmek P, Duprat C, Denis J, Faroux R, Renou C. Treatment of chronic hepatitis C with pegylated interferon and ribavirin in treatment-naïve patients in 'true life': a plea in favor of independent postmarketing evaluations. *Eur J Gastroenterol Hepatol*. 2010;22:1297–1302.
- Tohra SK, Taneja S, Ghosh S, et al. Prediction of sustained virological response to combination therapy with pegylated interferon alfa and ribavirin in patients with genotype 3 chronic hepatitis C. *Dig Dis Sci*. 2011;56:2449–2455.
- Pichetshote N, Groessl E, Yee H, Ho SB. Optimizing the dose and duration of therapy for chronic hepatitis C. *Gut Liver*. 2009;3:1–13.
- Ghany MG, Strader DB, Thomas DL, Seeff LB. American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49:1335–1374.
- Willems B, Hadziyannis SJ, Morgan TR, et al. Should treatment with peginterferon plus ribavirin be intensified in patients with HCV genotype 2/3 without a rapid virological response? *J Hepatol*. 2007;46:S6.
- Berg T, Shiffman ML, Zeuzem S, et al. 48 Weeks of peginterferon alfa-2a/ribavirin improves SVR24 and decreases relapse across HCV genotype 2/3 patient subgroups not achieving a rapid virological response: N-CORE study. *J Hepatol*. 2013;58:S323.
- 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;131:451–460.