What is the optimal duration of therapy in patients with hepatitis C genotype 2 or 3 infection ? : a review

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Abstract

Pegylated interferon plus ribavirin is the standard treatment for chronic hepatitis C (HCV). Even if genotype 2 and 3 patients only request a treatment of 24 weeks, this treatment remains very costly and difficult to tolerate due to numerous side effects.

Recently several studies focused on the possibility of further reducing treatment duration in chronic HCV genotype 2 and 3 patients without compromising sustained virological response (SVR).

Based on the available data, patients presenting a negative PCR at week 4 named a rapid virological response (RVR) probably are the best candidates to benefit from shorter treatment duration. In contrast patients without RVR should at least be treated for 24 weeks and retrospective data suggest that a more intensive or prolonged therapy for 48 weeks could be necessary.

However, at this moment it remains impossible to propose general recommendations for all patients with genotype 2 and 3.

Therefore more randomized prospective trials are needed to clarify several issues that are discussed in this review article. (Acta gastroenterol. belg., **2008**, 71, **298-302**).

Introduction

Current guidelines recommend that patients with chronic hepatitis C (HCV) genotype 2 or 3 should be treated with 24 weeks of pegylated interferon and ribavirin because the high sustained virological response rates (SVR) of 80% (1). These results seemed not to improve with longer duration of treatment of 48 weeks (2). Several recent studies investigated the possibility of further reducing treatment duration to achieve better compliance and lower costs without compromising the SVR rates. In contrast some patients mainly with genotype 3 manifest very high relapse rates (18-23%) (3,4) and maybe could benefit from prolonged therapy.

In this review we will focus on the data from published studies (full papers and abstracts) with the two currently approved forms of pegylated interferon alfa 2a and 2b comparing different treatment durations in genotype 2 and 3. Finally an algorithm for treatment of genotype 2 and 3 will be proposed taking into account the predictive factors of response and relapse.

1. *Shorter duration with Peg-IFN Alfa-2b*

In 2004, a first pilot study from Dalgard *et al.* (5) suggested that treatment can be shortened in most patients with genotype 2 or 3 who clear HCV RNA within the initial 4 weeks of therapy. In this non randomized study, 90% of patients who cleared HCV RNA by week 4 therapy presented SVR after 14 weeks of treatment with PEG-IFN-alfa-2b (1,5 µg/kg/week) plus ribavirin (800-1400 mg/day) .

These results were confirmed in a larger study by Mangia *et al.* (6). In this randomized trial, 283 patients were treated with PEG-IFN-alfa-2b (1,0 µg/kg/week) plus ribavirin (1000-1200 mg/day) either for a standard period of 24 weeks (control group) or for a variable 12 or 24 weeks depending on rapid virological response at week 4 (qualitative PCR under the detection limit of 50 IU/ml). Among rapid virological responders at week 4 (RVR), the SVR rate was not significantly different in patients treated for 24 weeks (91%) or 12 weeks (85%) but was low in non-RVR patients (60%). There were no differences in response rates between RVR genotype 2 or 3 but the number of genotype 3 was only 25%. Moreover the dose of PEG-IFN-alfa-2b was lower than that used in clinical practice (1,5 µg/kg/week) and in the previous study from Dalgard et al. Finally no predictive factor of RVR was found in multivariate analysis.

Recently, a non inferiority Norwegian study from Dalgard *et al.* (7) randomized 298 RVR genotype 2 (20%) or 3 (80%) patients between 14 weeks and 24 weeks of PEG-IFN-alfa-2b (1,5 µg/kg/week) plus ribavirin (800-1400 mg/day). The intention-to-treat analysis, showed no significant difference in SVR between 14 weeks and 24 weeks but there was a trend for higher SVR in the 24 weeks group (81,1% vs 90,7%). These results were quite similar in per-protocol analysis with only patients who received at least 80% of the planned treatment doses during at least 80% of the scheduled duration of treatment (91% SVR for 14 weeks, 95% SVR for 24 weeks). The authors concluded that the SVR rate after 14 weeks of treatment is high, and although longer treatment may give slightly better SVR, it is rational to treat patients with genotype 2 or 3 and who have a RVR for only 14 weeks because economical savings, good response to retreatment and fewer side effects.

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2. *Shorter duration with Peg-IFN Alfa-2a*

Von Wagner *et al.* (8) showed in a German multicenter study with 153 genotype 2 or 3 patients (treated with PEG-IFN alfa-2a 180 µg/week plus ribavirin 800-1200 mg/day) that the RVR was very high (93%) and that there was no statistical significant difference in SVR between total treatment duration for 16 weeks (82%) or 24 weeks (80%) in patients with RVR.

In this study patients with genotype 2 responded better than genotype 3 (92% versus 73% of SVR) and their SVR rates were independent from pretreatment viremia. In contrast patients with genotype 3 and high baseline viral load (> 800.000 IU/ml) manifested a higher relapse rate and lower SVR rate with reduced treatment (16 weeks) duration. However the difference in SVR did not reach statistically significance (67% for 24 weeks vs 55% for 16 weeks).

We can notify that in the latter study the dose of ribavirin was weight-based instead of the 800 mg/d used in clinical practice. Moreover the RVR was assessed with a detection limit of HCV RNA below 600 IU/ml and not with the 50 IU/ml currently used in routine.

In the largest randomized study from Shiffman *et al.* (3) including 1469 patients with genotype 2 or 3 treated with PEG-IFN alfa-2a 180 µg/week plus ribavirin 800 mg/day, the overall SVR was significantly higher ($p < 0.001$) in patients treated for 24 weeks (70%) compared to those treated for 16 weeks (62%) due to the higher relapse rate with shorter treatment (18% versus 31% $p < 0.001$).

The SVR rates however in patients with RVR were not significantly different between 24 weeks (85%) and 16 weeks (79%). Further analysis showed also that shorter treatment (16 weeks) is sufficient in patients with a low baseline HCV RNA (< 400 000 IU/ml).

This study suggests as the results published by the previous German study (8) that in patients with genotype 3 and high viral load (> 800 000 IU/ml), at least 24 weeks of treatment is probably necessary.

Recently Lagging *et al.* (9) showed in a large randomized study including G2 and G3 patients that 24 weeks of treatment of PEG-IFN alfa-2a 180 µg/week plus ribavirin 800 mg/day was associated with higher SVR than 12 weeks but it was suggested that in patients below 40 years 12 weeks of treatment could be sufficient (85% SVR for 12 weeks vs 92% for 24 weeks). This however needs to be confirmed particularly regarding the stage of fibrosis because it can be expected that younger patients have less severe fibrosis.

3. *Dose of ribavirin :*

The reduction of the treatment duration even in patients with RVR is likely to be accompanied by higher relapse rates. It is possible that higher doses of ribavirin as used in the German study (8) could prevent relapse after shorter treatment duration but no current study demonstrated that.

The importance of a sufficient dose of Ribavirin is also suggested in a recent sub analysis of the NORDynamic Trial presented in an oral communication at EASL 2008 (10). In this study Ribavirin concentration at week 4 was found to be an independent predictor of SVR. Higher ribavirin concentration (> 2 mg/dl) was associated with a significantly increased SVR.

Moreover in a recent study, Kalinowsky *et al.* (11) compared patients receiving a 12 week PEG-IFN alfa-2a 180 µg/week monotherapy followed by a 12 week combination therapy (with PEG-IFN alfa 2a 180 µg/week and ribavirin 800 mg/d) with patients receiving standard combination therapy for 24 weeks. They showed that there was a trend of higher SVR (85% vs 73%) for patients treated with longer ribavirin treatment (24 weeks vs 12 weeks), explained by a higher relapse rate in shortened ribavirin treatment (21% vs 8% $p < 0.005$).

This could at least in part explain that in the Shiffman (3) and more recent Lagging study (9) with PEG-IFN-alfa2a, using both fixed low dose of ribavirin (800 mg/d), overall results of shortened treatment were inferior compared to standard duration of treatment.

A large prospective randomized study comparing the efficacy of PEG-IFN alfa-2a 180 µg/w plus ribavirin 800 mg/d versus 1000-1200 mg/d in patients with genotype 2 and 3 and RVR is absolutely needed to demonstrate the optimal dose of ribavirin.

4. *Prognostic factors of SVR and rationale for adequate treatment duration :*

Patients with genotype 2 or 3 without RVR have a very low SVR with an abbreviated treatment regimen but even with the standard duration treatment (6-8). SVR is significantly impaired especially in patients with genotype 3 and high viral load (3,5,7) but Dalgard *et al.* (7) showed recently that if RVR is obtained little is gained by the prolongation of therapy beyond 14 weeks in these patients.

Previous trials have suggested that patients with genotype 3 and a high viral load may be in need of prolonged therapy or more intensive dose treatment (5,12). Willems *et al.* (4) re-analyzed data from two previous studies including patients with genotype 2 or 3 treated with PEG-IFN-alfa2a and different doses of rivavirin (800 mg/day or 1000-1200 mg/day) for different periods of time (24 or 48 weeks). Focusing on patients without RVR, the highest SVR rate (76%) and the lowest relapse rate (4%) occurred in patients treated with the high dose of ribavirin for 48 weeks.

However the number of patients recruited for analysis was small and therefore these interesting results need to be confirmed in prospective studies.

Recently at AASLD 2007 an interim analysis of a large German study (12) comparing 24 versus 48 weeks of treatment with PEG-IFN alfa 2b and weight-based doses of ribavirin in genotype 3 could not demonstrate a

Table 1. — **Milestones and relapse rate in G2 & G3**

Article	PEG-IFN Dose	RBV Dose	4-wks	RVR 12-16 wks	RVR 24 wks	No RVR 24 wks	No RVR 48 wks	Relapse (RR)
			RVR	SVR%	SVR%	SVR%	SVR%	
Mangia 2005 (n = 283)	1.0 µg/kg 12w vs 24 w	1000 or 1200 mg/day	63% < 50 IU	85%	91%	60%	NA	10% (12 -wk) 6-8% (24 -wk)
Zeuzem 2004 (n = 224)	1.5 µg/kg	800-1400 mg/day	78% G2 75% G3 < 29 IU	NA	94% G2 85% G3	89% G2 62% G3	NA	5-9% (G2) 8-23% (G3)
Dalgard EASL 2007, North-C (n = 428)	1.5 µg/kg 14w vs 24w	800-1400 mg/day	71% < 50 IU	81%	91%	55%	NA	11% (14 -wk) 5% (24 -wk)
Von Wagner, 2005 (n = 153)	180 µg/wk 16 w vs 24 w	800-1200 mg/day	93% < 600 IU	82%	80%	36% RR : 50%	NA	13% (16 -wk) 5% (24 -wk)
Shiffman, (n = 1469) NEJM 2007 ACCELERATE	180 µg/wk 16 w vs 24 w	800 mg/day	65% < 50 IU	79%	85%	26% (16 wk) 45% (24 wk)	NA	31% (16 -wk) 18% (24 -wk)*
Willems, EASL 2007 (Hadziyannis (H) and Fried (F))	180 µg/wk	800 or 1000/ 1200 mg/day	75% (H) 59% (F)	NA		67% (800) 65% (1000-1200)	67% (800) 76% (1000-1200)	26% (24w -800) 24% (24w -1000 - 1200) 13% (48w -800) 4% (48w -1000 - 1200
Lagging, EASL 2007 (n = 340)	180 µg/wk	800 mg/day	NR	56% (G2) 65% (G3)	87% (G2) 83% (G3)		NA	NR

difference in SVR regardless of the presence of low or high baseline viral load (> 600.000 IU/ml) confirming the findings of the Hadziannis study (2) but RVR was not taken into account.

In the largest study (3), lower pretreatment HCV RNA level (< 400.000 IU/ml), lower weight (< 80 kg) and absence of bridging fibrosis or cirrhosis were predictive of SVR for genotype 2 and 3 in multivariate analysis. Treatment of 24 weeks predicted a SVR only in patients with genotype 2 but not in genotype 3 especially in patients without RVR.

During the last EASL meeting Mangia *et al.* (14) showed in a large cohort of genotype 2 and 3 patients achieving RVR that BMI > 27 kg/m^2 and/or platelets < 140.000 mm^3 were independent predictive factors of relapse after a 12 week treatment of PegIFN alfa 2b (1,5 µg/kg) and ribavirine (1000-1200 mg). These data also suggest that in the subgroup of patients with markers of advanced fibrosis standard treatment duration of 24 weeks should be reserved even if there is a RVR. Finally a Scandinavian study (15) found that 12 weeks of PegIFN alfa 2a 180 µg/week and ribavirin 800 mg/d was inferior to 24 weeks in genotype 2 as well as in genotype 3 patients with steatosis recommending that those patients should be treated for 24 weeks.

5. *Difference between Genotype 2 and 3 :*

Mangia *et al.* (6) observed no statistical difference in SVR between 12 weeks and 24 weeks of treatment and between genotype 2 and genotype 3 patients with a RVR. However in patients without RVR treated for 24 weeks SVR rates were significantly better in genotype 2 compared to genotype 3. Data have to be taken with caution because majority of patients (n = 213) were genotype 2 and only 70 patients (17 in standard duration therapy) with genotype 3 were recruited.

In the German study (8), SVR were higher in genotype 2 (92%) than in genotype 3 (73%) but number of genotype 2 was rather small (n = 38). Moreover high baseline viral load (> 800.000 IU/ml) only affected SVR in genotype 3. In multivariate analysis of all patients, genotype 2, low viral load (< 800.000 IU/ml) and low gamma-GT value were independent factors of SVR. Fibrosis score and GGT were also slightly higher in patients without RVR but did not reach statistical significance.

Overall, studies report higher SVR in genotype 2 compared to genotype 3 whatever the duration of therapy. Concerning the duration of treatment, the largest study (3) showed that mainly genotype 2 patients especially those presenting no RVR seemed to benefit from standard duration of treatment (24 weeks).

Recently a randomized study (16) suggested that the need for 24 weeks of treatment could be overcome in patients with genotype 2 by using higher doses of ribavirin (1000-1200 mg/d).

6. *Algorithm*

Discussed studies are resumed in table 1.

Based on these data an algorithm is proposed in figure 1.

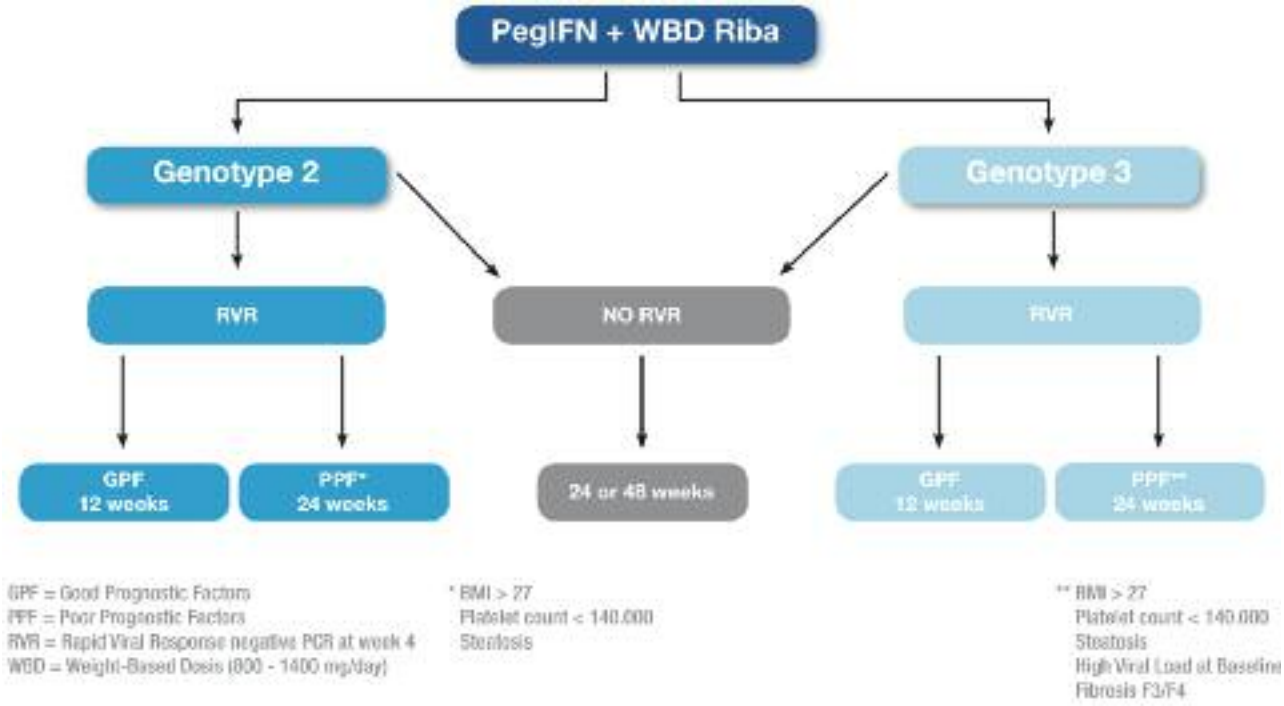

Fig. 1. — Proposed algorithm for management of genotype 2 and 3 patients

Conclusion

Evidence has recently accumulated that at least a subgroup of genotype 2 and

3 patients could benefit from shorter treatment duration without compromising SVR.

Available data seem to favour RVR as the most reliable factor to identify those patients. Other predictive factors as low baseline viremia, absence of significant fibrosis, absence of steatosis, platelet count < 140.000 mm^3 also seems to play a role but more data are necessary.

On the other hand patients with genotype 2 and 3 without RVR should at least be treated for 24 weeks. It may be even justified to treat them with a prolonged and/or intensified treatment schedule. Currently only retrospective data are available and prospective randomised trials are necessary to clarify this issue.

Due to different treatment schedules (regarding duration or dosage of Pegylated-IFN alfa-2b and ribavirin) and the different non inferiority margins used to assess the efficacy of shorter treatment duration in the several studies, it is at this moment difficult to propose general recommendations for all patients with genotype 2 and 3.

More randomised, prospective trials are needed to determinate the optimal reduced duration of therapy (12, 14 or 16 weeks), the best level of low viral load (< 400.000, < 600.000 or < 800.000 IU/ml) and the optimal doses of PegIFN –alfa-2b and ribavirin.

This will allow in the future to further tailor treatment and avoid over- or under treatment.

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