

REVIEW

Pegylated-interferon and ribavirin in liver transplant candidates and recipients with HCV cirrhosis: systematic review and meta-analysis of prospective controlled studies

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SUMMARY. Pegylated interferon with ribavirin (Peg/R) is the most effective therapy for chronic hepatitis C virus (HCV) but its utility and effectiveness after liver transplantation has been difficult to assess. We evaluated efficacy, tolerability, and safety of Peg/R in liver transplant candidates and recipients with HCV cirrhosis. We searched medical databases and conference proceedings between January 1999 and January 2008 selecting randomized and nonrandomized studies. Primary end points meta-analytically were: (1) sustained viral response (SVR) and (2) histological response. Secondary end points were: (1) treatment discontinuation, (2) mortality, and (3) rejection episodes. Pegylated interferons using either 1–1.5 mcg/kg of pegylated interferon alpha-2b or 180 µg (pegylated interferon alpha-2a combined with ribavirin 800–1200 mg/day were the most effective compared to any

other regimen or no therapy. In three pretransplant studies the median SVR was 19.6% (19.6–50%). In six postransplant studies where a meta-analysis was done the cumulative risk difference in SVR was 0.31% (95% CI, 0.18–0.44, $p < 0.001$). However histological response was not significantly better compared to no therapy or other antiviral regimens. There were no significant differences in discontinuation of therapy, acute or chronic rejection or mortality between optimal Peg/R vs no treatment or other regimens. Hence pegylated interferon plus ribavirin in full doses is effective pre and post transplant but has a low SVR rate. To date no significant histological improvement has been reported.

Keywords: cirrhosis, HCV, pegylated interferon, ribavirin, transplantation.

INTRODUCTION

Hepatitis C virus (HCV) reinfection is a major problem in liver transplantation for HCV related cirrhosis [1]. Between 8% and 30% of patients progress to cirrhosis within 5 years and thereafter over 3 years, the cumulative risk of complications is 65% [2].

Different antiviral therapeutic strategies have been used before and after liver transplantation (preemptive therapy or for recurrent disease). In 2005 we reported [3] better sustained virological response (SVR) rates for interferon with ribavirin combination therapy compared to interferon monotherapy (43% vs 12.5%), but little data existed for peginterferon alpha-2a or alpha-2b and ribavirin, which

was already the standard treatment for nontransplanted patients with chronic hepatitis C [4–6], providing an incremental advance over a combination of standard interferon with ribavirin, with a similar side-effect profile. Other reviews published in 2006 and 2007 confirmed our previous findings [3] and again indicated that data regarding pegylated interferon and ribavirin were still scanty [7–9]. Wang *et al.* [8] found that the SVR for pegylated interferon and ribavirin was 27%, vs 24% for standard interferon and ribavirin after liver transplantation. However the results were pooled mainly from uncontrolled trials with only three prospective studies, one randomized [10], one nonrandomized [11] with standard interferon, and one nonrandomized study [12] with pegylated interferon. Thus due to the lack of published prospective studies, the true benefit from pegylated interferon and ribavirin in liver transplant candidates and recipients with HCV cirrhosis remained unclear.

Our aim was to perform a systematic review and a meta-analysis when appropriate to assess efficacy, tolerability, and

Abbreviations: GF, growth factors; HCV, hepatitis C virus; HR, histological response; SVR, sustained viral response.

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safety of pegylated interferon and ribavirin in liver transplant candidates and recipients.

METHODS

Data identification

We searched Medline and Cochrane library from January 1999 to January 2008 for English and non-English publications using text words 'transplantation', 'cirrhosis', 'HCV', 'antiviral therapy', 'PEG or pegylated interferon', 'ribavirin'. We manually searched (P.M., A.S. and V.C.) references from review articles and original studies and all abstracts from the International, American, European, and Asian-Pacific associations for the Study of Liver Diseases meetings, those from the American Digestive Diseases Week, the United European Gastroenterology Week and the International Transplantation Liver Society and the European Society for Organ Transplantation. We checked on duplication of abstracts, and abstracts subsequently published as full papers.

Inclusion criteria

Studies included for analysis needed to fulfil the following criteria: (i) published as abstract or full paper, (ii) prospective controlled or randomized controlled design, (iii) participants were cirrhotic candidates for liver transplantation or transplanted patients with hepatitis C detected by a sensitive method, (iv) therapy with pegylated interferon alpha-2a or alpha-2b and ribavirin, (v) combination therapy was to be used for at least 24 weeks, (vi) SVR rate was stated, (vii) excluded mixed sequential regimens containing pegylated interferon only in part, (viii) excluded patients co-infected with HIV or HBV, and (ix) excluded patients with cirrhosis not considered for transplantation.

Data extraction

Data were extracted independently by P.M., A.S. and V.C., tabulated according to intention to treat using a predefined review form. The decision to include or exclude a study was made before the meta-analysis was carried out and agreed by consensus amongst the authors. In the present review agreement between reviewers for selection of articles for all analyses was 100%.

End points for analysis

Separate analyses were made for therapy in liver transplant candidates and after transplantation administered either pre-emptively or for recurrent HCV disease.

Pre-emptive treatment was defined as starting during the first weeks post-transplant with no histological or biochemical flares indicating recurrent hepatitis. Recurrent disease was defined as elevated serum alanine amino-

transferase levels for 6 months or more and histological evidence of HCV recurrence showing lobular hepatitis and fibrosis.

To assess the efficacy of pre-transplantation or post-transplantation treatment protocols, we used SVR as the main outcome, defined as undetectable HCV-RNA in blood by PCR techniques, 6 months after the end of treatment. An additional outcome measure of efficacy, used only for the post transplant setting, was histological response (HR), assessing histology from 6 to 12 months after the end of treatment. Histological response was defined as the same stage or a decrease of at least one point (or stage) in the overall histological score, compared to pre-treatment biopsy.

Safety of treatment was evaluated considering: (i) discontinuation of treatment, (ii) mortality, (iii) acute rejection episodes, (iv) chronic rejection, and (v) *de novo* autoimmune complications.

The proportion of naive or previously treated patients and the use of growth factors were reported descriptively. If a small number of studies limited evaluation by meta-analysis, only a descriptive evaluation was performed. Outcomes were evaluated with respect to the publication year and the use or not of randomization.

Assessment of methodological quality and publication bias

Three authors (P.M., A.S. and V.C.) independently assigned a quality score [13] only for randomized controlled trials if published as full papers. Publication bias was assessed by funnel plots of the primary outcome against sample size.

Statistical analysis

When a meta-analysis was appropriate the random effects model was used as we expected differences in the different study protocols. Risk difference (absolute risk reduction) was the main effect measure, to facilitate comparison across groups [14]. Heterogeneity was assessed using the *Q* test ($P < 0.1$), evaluating whether the treatment effect variation across groups was greater than expected. A I^2 test, which does not depend on the number of studies, the type of outcome data, or the choice of treatment effect, was also used to assess heterogeneity.

All statistical analyses and plots were carried out using a published and validated computer program [15].

RESULTS

Treatment of liver transplant candidates

Descriptive assessment. There were 10 relevant articles: four full articles [16–19] and six abstracts [20–25]. However only two randomized [17,19] and one controlled but nonrandomized trial [18], comprising 335 patients, met

the inclusion criteria. All three were published as full articles [17–19] (Table 1).

Exclusions were three prospective noncontrolled studies [20,22,25] and four retrospective evaluations [16,21,23,24].

Quality assessment of the two randomized studies gave a score of five [17] and three [19]. Each study included a different comparison group. Treatment groups fulfilled the inclusion criteria regarding combination treatment but with different protocols regarding dose schedule (Table 1). Previous treatment, discontinuation of treatment due to adverse events end of follow-up mortality and transplantation is shown in Table 1. In one growth factors were used [18] and in another they were not [19].

Efficacy

Sustained virological response. In total, 181 patients were treated with either pegylated interferon and ribavirin 800 to 1200 mg for either 24 weeks followed by another 24 weeks if HCV–RNA was negative (at 24 weeks), or treated for 52 weeks (group A); 174 had either no treatment ($n = 63$) [18], or pegylated interferon alpha-2a or alpha-2b combined with low ribavirin dose ($n = 60$) [17], or pegylated interferon monotherapy ($n = 51$) [19] (group B). SVR rates were 19.6% [18], 19.6% [19] and 50% [17] for group A and 0% [18], 9.8% [19] and 38.3% [17] for group B (means 30.4% group A, 16.1% group B).

Patients with genotype 1 had lower SVR rates: 12.5% [19] (summarized for both treatment arms), 7% [18], and 32% [17] (the latter two studies report genotype 1 and 4 combined). The relative percentages of SVR for genotypes 2 and 3 were higher ranging from 43.5% to 72%.

Safety

Discontinuation of treatment. In the two randomized controlled studies combination treatment was compared to either pegylated interferon monotherapy or a low dose ribavirin regimen. In the first [19], discontinuation occurred in 27.4% with combination therapy, which was 11.8% less in comparison to monotherapy, but not statistically significant.

Interestingly in the second study [17], the discontinuation rate was 23.4%, and the percentage difference was 3.2% but this was less than the first study despite high ribavirin dosage, indicating that discontinuation of therapy was determined by interferon.

Another study [18] compared combination therapy vs no treatment in which 19.6% discontinued therapy. Only this study reported the use of growth factors.

Mortality. Only two studies [17,18] reported data on mortality. No deaths occurred in the high dose arm and two in the low dose arm in one [17], whereas the number of

Table 1 Comparative studies of pegylated interferon and ribavirin in liver transplant candidates with HCV related cirrhosis

First author, year, type of study, [Ref]	Patients	Previous treatment	Current treatment	SVR (%)	Discontinuation of treatment	End of follow-up mortality	Transplanted
Di Marco 2005	102	67% naïve and 33% prior INF	(a) PEG-IFN 1.0 mcg + RBV 800 mg for 26 + 26 if HCV-RNA negative	(a) 19.6	(a) 14/51	NR	NR
RCT [19]			(b) PEG-IFN 1.0 mcg	(b) 9.8	(b) 20/51		
Helbling 2006	124	Naïve	(a) PEG-IFN 180 µg and HIGH-RIBA 1000 to 1200 mg for 48 weeks	(a) 50	(a) 15/64	(a) 0/64	NR
RCT [17]			(b) PEG-IFN 180 µg and LOW-RIBA 600 to 800 mg	(b) 38.3	(b) 16/60	(b) 2/60	
Iacobellis 2007	129	Naïve or prior INF	(a) PEG IFN 1.0 µg + rb 0.8 to 1.0 g for 24 weeks	(a) 19.6	(a) 13/66	(a) 5/66	(a) 1
NRT [18]			(b) no treatment	(b) 0	(b) 0/63	(b) 4/63	(b) 4

NRT, nonrandomized trial; RCT, randomized controlled trial; abs, abstract; PEG-INF, pegylated interferon; INF, interferon; RIBA, ribavirin.

deaths that occurred after completion of therapy in the other study [18] was similar between the study groups, a difference of only 1.2%. Interestingly in this latter study, long term survival was also assessed over a median follow up of 30 months (range 4–38) after the end of therapy: 15 deaths in non-treated patients, and 9 in treated ones. Liver transplantation was performed in four and one patients respectively.

Post transplant prophylactic or preemptive treatment

There were four articles. None fulfilled inclusion criteria: one randomized study used standard interferon alpha-2b in some patients, but these could not be differentiated from those who received pegylated interferon and ribavirin [26]; one prospective not controlled [27]; and two retrospective studies [28,29].

Post transplant therapy of recurrent HCV disease

Descriptive assessment. There were 35 relevant articles: 20 [12,30–48] were full papers and 15 abstracts [49–63]. The studies fulfilling inclusion were: four randomized [43,46,49,52] and two nonrandomized trials [12,37] involving 264 patients [four full papers, and two abstracts (Table 2)]. The excluded studies were: 14 prospective but not controlled [30–33,35,38,42,44,45,48,53,54,56,62], one prospective study [47] in which a multiple therapeutic regimen was used (standard interferon for 3 months and then pegylated interferon and ribavirin for 9 months vs standard interferon and ribavirin), one study in which patients completed 52 weeks of combination therapy and then randomized to receive ribavirin alone or no therapy for another 48 weeks [63], and 13 retrospective studies [34,36,39–41,50,51,55,57–61].

In the studies included for evaluation, the comparison groups were heterogeneous: three included a nontreated group [12,37,46], two used low dose pegylated interferon and ribavirin [49,52], and one used standard dose pegylated interferon monotherapy [43]. In four studies, growth factors were used [12,37,46,49], in one they were not [43], and in one it was not reported [52]. Four studies did not report if patients were previously treated [12,46,49,52] whereas one included only previously treated patients (standard interferon and ribavirin) [43], and another study used only naïve patients [37]. The start of treatment criterion was disease recurrence in all studies (Table 2), and treatment was started between a mean of 3.8 to 44 months across the studies. Two studies [43,46] set a time limit to start treatment of between 6 and 12 months post transplant as an inclusion criterion. Other study characteristics are shown in Table 2.

Quality assessment of two published randomized studies gave one a score of three [46] and one of four [43]. Test of funnel plot asymmetry suggested no publication bias ($\alpha = 2.42$, 95% CI = $-5.11/0.28$, $P = 0.08$) (Fig. 1).

Efficacy.

Sustained virological response: In total, 140 patients [12,37,43,46,49,52], were treated with either Peg interferon using 180 µg (alpha-2a) or 1.5 mcg/weekly (alpha-2b) and Ribavirin 800–1200 mg, either *ab initio*, or an increasing dose from a low baseline for either 48 or 24 weeks (continued for another 24 weeks if HCV RNA was negative) – this is group A.

Group B consisted of 124 patients either not treated or treated with low dose pegylated interferon regimen (0.5 mcg/weekly) with ribavirin, or only pegylated interferon monotherapy. Median sustained virological response was 41% (range 29.6–77.7%) for group A and 9.2% (range 0–50%) for group B (means 42% group A and 11% group B) (Table 2). The absolute risk difference in favour of group A was 0.31 (95% CI, 0.18–0.44, $P < 0.001$) (Fig. 2). Heterogeneity was significant result ($Q = 9.671$, $P = 0.085$, $df = 5$, and I^2 was 58.6%). Thus a cautious approach is needed to interpreting the combined estimate of risk difference for these studies. In both groups A and B the interval of starting antiviral therapy from the date of transplantation did not influence the likelihood of SVR.

Subgroup analyses: Best combined treatment was evaluated vs no treatment and/or any other antiviral combination. Due to the small number of trials and patients it was not possible to further subdivide the ‘any other antiviral treatment’ group.

Patients with genotype 1 (Table 2) comprised between 69% and 100% of cohorts, so a subgroup analysis for genotype 1 vs non 1 was not feasible.

As there were only two abstracts selected for evaluation there was no need to evaluate either abstracts vs full publications, or with respect to year of publication (all studies published between 2005 and 2007) (Table 2).

The results of subgroup analyses for SVR in relation to type of trial, use of growth factors (GF), pegylated interferon with ribavirin vs no treatment or any other treatment (whether this was monotherapy or combination therapy) are shown in Fig. 3. Estimates of SVR using the random effects model for all these subgroups were similar to those of the main meta-analysis in all except two. These were the subgroups including ‘any other treatment’, and ‘no GF use’. In both subgroups, the study causing heterogeneity was by Angelico *et al.* [43], as that by Gordon *et al.* [49] had a very small sample size. Looking more in detail this study, where SVR rate was in favour of Peg-interferon monotherapy, we think that the lack of growth factors reduced greatly the potential effect of combination therapy as the mean concentrations of ribavirin achieved (435 ± 114 mg/day) were low. Additionally among 8/21 patients who managed to receive the full dose (800 mg/day) of ribavirin six needed a dose reduction.

Table 2 Comparative studies of pegylated interferon and ribavirin in patients transplanted for HCV related cirrhosis with recurrent disease

First author, year, type of study, [Ref]	Patients	Treatment	SVR (%)	Months from OLT to start treatment mean (range or SD)	Genotype 1 (%)	Viral load at baseline (IU/ml)	Immunosuppressive drug regimen
Castells 2005	48	(a) PEG-IFN 1.5 mcg + RBV 600 to 800 mg for 24 + 24 weeks if RNA neg	(a) 33.3	3.8 (+/-2.2)	100	6.1-6.5 × 10 ⁷	TAC + STER in 17/TAC + STER + MMF in 5
NRT [12]		(b) no treatment	(b) 0				
Gordon 2005	13	(a) PEG-IFN 1.5 mcg + RBV 400 to 800 mg for 52 weeks	(a) 77.7	44 (11-144)	69	2.51 × 10 ⁶	Cy A in 1/TAC in 12
RCT-abs [49]		(b) PEG-IFN 0.5 mcg + RBV 400 to 800 mg for 52 weeks	(b) 50				
Ghalib 2006	59	(a) PEG-IFN 1.5 mg + RBV 600mg turned to 800mg at week 4, (high dose arm) for 24 + 24 if RNA neg.	(a) 59.3	18 (3-61)	73	3.9 × 10 ⁶	NR
RCT-abs [52]		(b) PEG-IFN 0.5 mg + RBV 600 mg turned to 800 mg at week 4 (low dose arm)	(b) 18.5				
Bizollon 2007	48	(a) PEG-IFN 1.5 mcg + RBV 800 to 1000 mg for 48 weeks	(a) 29.6	NR	79	5.81-5.89 log10	Cy A based reg in 23/TAC based in 25/MMF 9
NRT [37]		(b) no treatment	(b) 0				
Carrión 2007	54	(a) PEG-IFN 1.5 mg + RBV 800mg for 48 weeks	(a) 48	17 (9-38)	85	6.4-6.6 log 10	Cy A in 37/TAC in 41
RCT [46]		(b) No treatment	(b) 0				
Angelico 2007	42	(a) PEG-IFN 180 mg + RBV 200mg increased 100mg every 15 days up to maximum tolerated dose for 48 weeks (LADR)	(a) 33.3	44 (12-96)	83	156-194 × 10 ⁴	Cy A in 16/TAC in 23/nothing in 3
RCT [43]		(b) PEG-IFN 180 mg	(b) 38				

NRT, nonrandomized trial; RCT, randomized controlled trial; abs, abstract; PEG-IFN, pegylated interferon; INF, interferon; RIBA, ribavirin; Cy A, cyclosporine; TAC, tacrolimus; MMF, mycophenolate mofetil; STER, steroids.

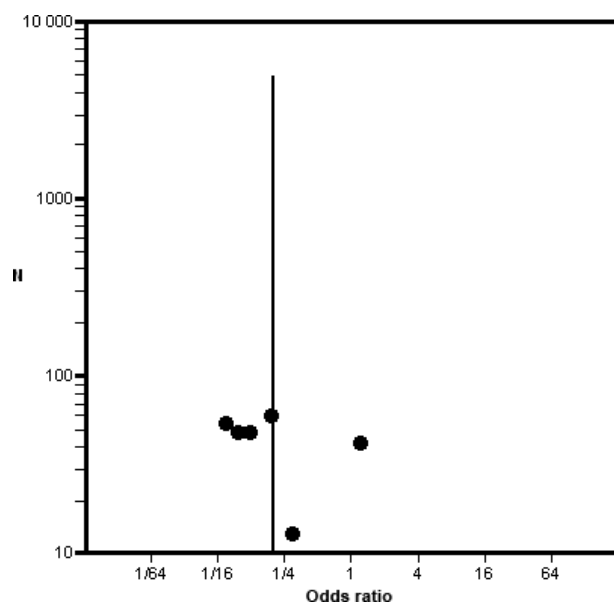


Fig. 1 Funnel plot diagram of comparative studies of standard dose pegylated interferon and ribavirin vs no therapy or other antiviral combinations used to treat patients transplanted for HCV related cirrhosis with recurrent disease. No publication bias is shown ($P = 0.08$).

In conclusion this subgroup analysis shows that the benefit of combination therapy is significant compared to no treatment but not significant compared to any other treatment.

Histological response: There were three studies, two randomized [43,46] and one nonrandomized [37], all full papers. Group A and B were defined as for the SVR analysis. Group A comprised 75 patients (Peg/Ribavirin treatment) and group B comprised 69 patients. The histological response was 64% for group A and 32% for group B. The absolute risk difference was in favour of group A, but it did not reach statistical significance: 0.26 (95% CI,

0.24–(–1.09), $P = 0.2$). Heterogeneity was significant ($Q = 34.26$, $P < 0.001$, $df = 3$ and I^2 was 94.2%). The Forrest plot diagram is shown in Fig. 4.

Safety.

Discontinuation of treatment: A meta-analysis was not performed, as in three studies [12,37,46] the control group was not treated. However discontinuation rates in the treatment groups were very variable despite the use of growth factors: 0% [12], 7% [37] and 22% [46]. In another study [49] discontinuation was not reported separately for each treatment group.

In the last two studies selected for evaluation [43,52] there was no statistical difference between different groups. In the study by Ghalib *et al.* the discontinuation rate was 15.6%, for the group of patients treated with standard dose pegylated interferon and ribavirin, and 14.8% for those on low pegylated interferon and ribavirin [52]. The highest rate of discontinuation (28.5% for pegylated interferon/ribavirin vs 23.8% for pegylated interferon monotherapy) was reported by Angelico *et al.* [43], who did not use growth factors.

Acute rejection episodes: In four of the six studies acute rejection episodes were reported separately for each treatment group: two were randomized [43,46], two nonrandomized studies [12,37] all full papers. Patients were assigned to group A ($n = 99$) and group B ($n = 93$) as for the SVR analysis.

Pooled percentages were 5% for group A and 6.4% for group B. The absolute risk difference was 0.010 favouring group B (95% CI, 0.028 – (–0.36), $P = 0.7$). There was no significant heterogeneity between studies ($Q = 2.5$, $P = 0.4$, $df = 3$ and I^2 was 21.5%). The Forrest plot diagram is shown in Fig. 5.

Chronic rejection and autoimmune complications: Another endpoint conspicuously absent from the selected studies was chronic rejection [62], only reported in one study [37], in two

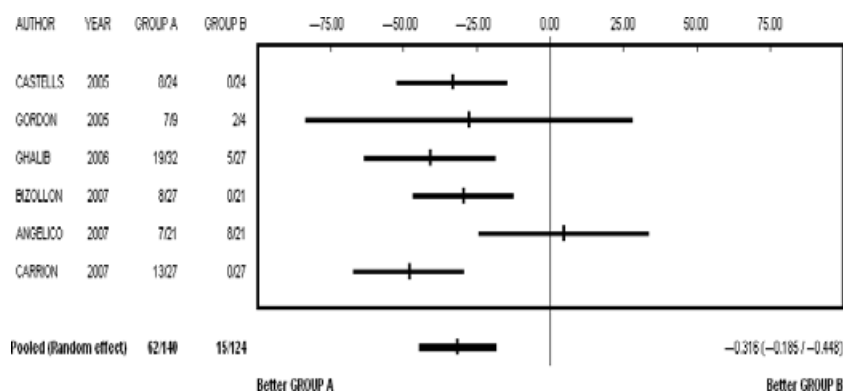


Fig. 2 Forrest plot of sustained viral response rates in comparative studies of standard dose pegylated interferon and ribavirin vs no therapy or other antiviral combinations in patients transplanted for HCV related cirrhosis with recurrent disease.

Group A: pegylated interferon alpha-2a 180 μ g or alpha-2b 1.5 mcg plus ribavirin 800 to 1200 mg. Group B: no treatment or low dose pegylated interferon plus ribavirin or pegylated interferon monotherapy.

Fig. 3 Subgroup analyses of sustained viral response rates following therapy with standard dose pegylated interferon and ribavirin vs no therapy or other antiviral combinations in patients transplanted for HCV related cirrhosis and recurrent disease. Group A: pegylated interferon alpha-2a 180 µg or alpha-2b 1.5 mcg plus ribavirin 800 to 1200 mg. Group B: no treatment or low dose pegylated interferon plus ribavirin or pegylated interferon monotherapy. GF, growth factors; REM, random effects model; FEM, fixed effects model.

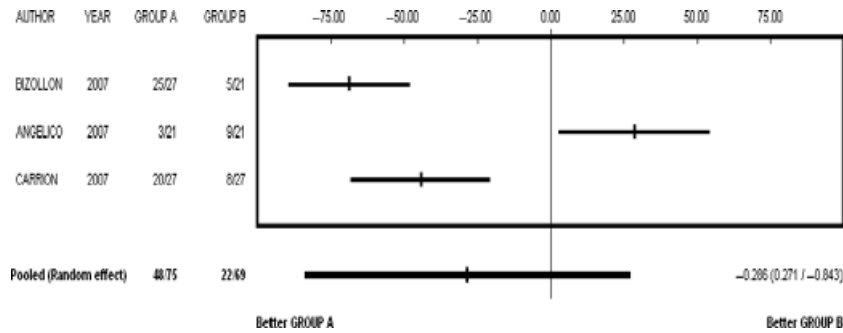
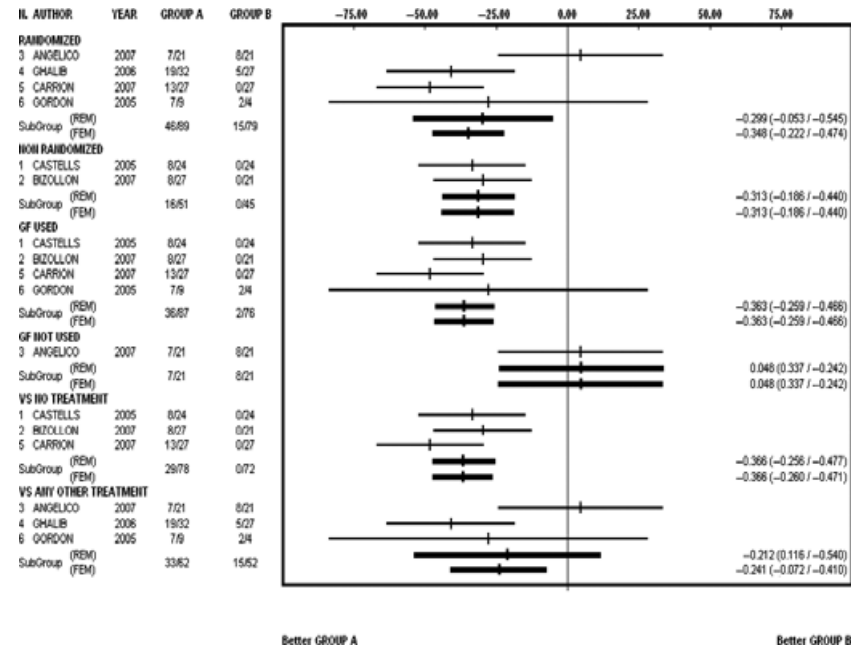


Fig. 4 Histological response (HR) rates following therapy with standard dose pegylated interferon and ribavirin vs no therapy or other antiviral combinations in patients transplanted for HCV related cirrhosis with recurrent disease. Group A: pegylated interferon alpha-2a 180 µg or alpha-2b 1.5 mcg plus ribavirin 800 to 1200 mg. Group B: no treatment or low dose pegylated interferon plus ribavirin or pegylated interferon monotherapy.

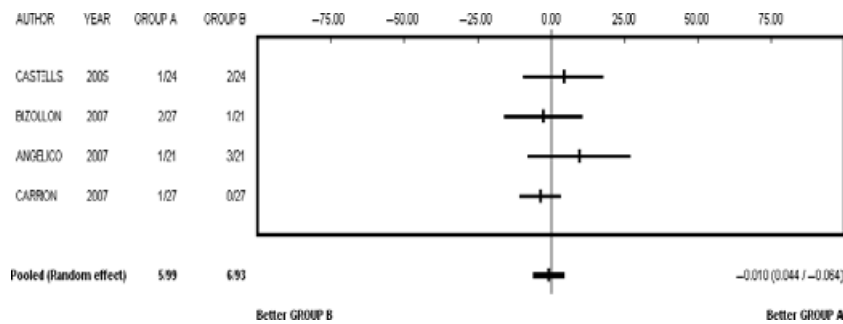


Fig. 5 Forrest plot of the occurrence of acute cellular rejection in comparative studies of standard dose pegylated interferon and ribavirin vs no therapy or other antiviral combinations in patients transplanted for HCV related cirrhosis with recurrent disease. Group A: pegylated interferon alpha-2a 180 µg or alpha-2b 1.5 mcg plus ribavirin 800 to 1200 mg. Group B: no treatment or low dose pegylated interferon plus ribavirin or pegylated interferon monotherapy.

patients, who had received pegylated interferon and ribavirin, developing chronic rejection 4–6 months after the end of treatment. Interestingly both patients had achieved SVR. No cases of *de novo* autoimmune hepatitis were reported although this has been described in case reports [64,65].

Mortality: In five of the six studies, mortality was reported separately for each group. Three were randomized evaluations, two full papers [43,46] and one abstract [52] and two nonrandomized studies as full papers [12,37]. In total, 131 patients were assigned to group A and 120 patients to group B, as for the SVR analysis.

Two studies [37,43] did not report any deaths, do not contribute to the pooled result and are excluded from the Forrest plot (Fig. 6).

The percentages were 7% for group A and 5% for group B. The absolute risk difference was 0.042 favouring group B (95% CI, 0.027–(–1.55), $P = 0.1$). There was no significant heterogeneity between the studies ($Q = 0.92$, $P = 0.6$, $df = 3$).

DISCUSSION

The present review and meta-analysis shows that the effect of pegylated interferon with ribavirin, in optimal, standard doses is efficacious, in both liver transplant candidates, and in recipients, to treat recurrent HCV disease. However it is associated with a low median SVR of 19.6% (19.6–50%) in liver transplant candidates, and 41% (29.6–77.7%) in those with recurrent disease after liver transplantation.

Assessing histological response by biopsy performed at 6 months to 1 year after the end of treatment did not demonstrate statistically significant differences using pegylated interferon with ribavirin, vs any other treatment, or no treatment. This could be due to the short intervals to performing biopsies after end of therapy, but clearly is an important endpoint which must be explored in future reports.

In liver transplant candidates treatment with Peginterferon alpha-2b (1.0 mcg/kg) or alpha-2a (180 µg) and

ribavirin 800–1200 mg for 24–52 weeks was better than any other option.

In post-transplant patients with recurrent HCV disease, combination Peg alpha-2b (1.5 mcg/kg) or alpha-2a (180 µg) and ribavirin 800–1200 mg either *ab initio* or as an increasing dose regimen for 48 or 24 weeks (continued for another 24 weeks if HCV RNA was negative) was significantly better than no therapy but not than any other therapy. Histological response was not significantly better in groups with the best SVR. Importantly the analysis regarding discontinuation of therapy, frequency of acute or chronic rejection, and mortality did not demonstrate significant differences. This suggests a reasonable safety profile of Peg interferon and ribavirin, presumably aided by intensive and close follow up of patients. In the evaluation of the studies included in our analysis there was no relationship of the interval between the time of transplantation and start of antiviral therapy. Theoretically there could be a decreasing viral load when immunosuppression is reduced for long term maintenance therapy and the viral load at start of therapy could influence the SVR response. However there was no data available to evaluate this particular point.

In chronic hepatitis C most studies indicate that HCV genotype and the ability to tolerate the full dose and duration of therapy are the major predictors of virologic response. In the study in which only 44% of patients had genotype 1 [17] the SVR rate was the highest at 50%, in comparison with an SVR rate of 19.7% in a cohort with genotype 1 in 67% [18], and 19.6% SVR in a cohort with genotype 1 in 86% [19].

There were no studies regarding preemptive therapy that satisfied inclusion criteria for this meta-analysis. Nevertheless the number of reports indicates this kind of approach is the least studied.

Post-transplant recurrent disease is the preferred setting to offer antiviral HCV therapy, as most studies were in this group. This is likely to be so for a number of reasons: (1) recurrent hepatitis is often seen to be worsening only after the first year from transplant, and this is when the risk of rejection is lower and graft function is better, and lower

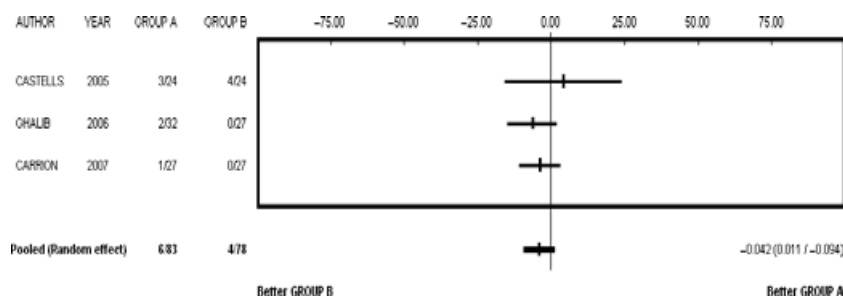


Fig. 6 Forrest plot of mortality in comparative studies of standard dose pegylated interferon and ribavirin vs no therapy or other antiviral combinations in patients transplanted for HCV related cirrhosis with recurrent disease. Group A: pegylated interferon alpha-2a 180 µg or alpha-2b 1.5 mcg plus ribavirin 800 to 1200 mg. Group B: no treatment or low dose pegylated interferon plus ribavirin or pegylated interferon monotherapy.

immunosuppressant drug dosages are usually used, (2) there is probably a better risk/benefit ratio for therapy given later on after transplantation, as at this time there are likely to be fewer patients who may be most at risk for severe inflammation and fibrosis from HCV recurrence (i.e. excluding those with complications during the first year).

However the low SVR rate which is documented in the post transplant population is still a drawback for the choice to treat or not to treat. Potential factors that influence this low SVR rate are: (1) high percentage of patients with genotype 1 virus, (2) high viral load at start of treatment, (3) high percentage of prior nonresponders to therapy, (4) side effects that often make the use of standard doses and duration of treatment difficult, (5) the use or not of growth factors, and (6) the effect of immunosuppression.

In the analysis, the studies included had 69% to 100% of patients with genotype 1. Two studies that had genotype 1 patients [12,37] either with a mean viral load of $6.1-6.5 \times 10^7$ IU/mL or $5.81-5.89 \log_{10}$ IU/mL, used growth factors. In both the SVR rate was 30%. In addition one study [37] all patients had been previously treated post transplant with standard interferon and ribavirin for at least 24 weeks. In contrast, in a study using a low Peg interferon regimen, 81% were nonresponders [52] but growth factors use is not reposted. However Angelico *et al.* [43] reported the highest SVR rate in their Peg interferon monotherapy group, and not with combined therapy, treating patients naïve to prior therapy, and with a low initial viral load. Growth factors were not used, perhaps making the use of ribavirin less effective.

The present meta-analysis does give some indication of the efficacy of combined pegylated interferon and ribavirin in liver transplant candidates and after liver transplantation. However the number of studies and patients included in each study was small and the comparison groups were not homogeneous. In addition the follow up was not sufficiently long in order to clarify whether histological improvement would occur. This limits the robustness of the estimate of benefit, and the assessment of clinical effectiveness which is the balance of risk/benefit.

Thus randomized studies designed as multicentre evaluations are still needed, and they should report on prolonged follow up, using optimal measures to achieve and maximise the tolerated doses of pegylated interferon and ribavirin. This will allow a much better estimate of effectiveness. New agents against HCV may also further improve therapeutic efficacy and tolerability in this difficult group of patients and need to be studied as soon as possible.

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