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Maintenance interferon therapy in chronic hepatitis C patients who failed initial antiviral therapy
A meta-analysis

Hung-Chang Hung, MD, PhD[a,b], Hsien-Hua Liao, MD, PhD[c,d], Shiuan-Chih Chen, MD, PhD[c,e], Shih-Ming Tsao, MD, PhD[c,f], Yuan-Ti Lee, MD, PhD[c,f,*]

Abstract

Objectives: To evaluate the effect of pegylated interferon maintenance therapy in patients with chronic hepatitis C who failed initial antiviral therapy.

Methods: This is a meta-analysis of 6 randomized controlled trials that met the eligibility criteria. In all, 2438 chronic hepatitis C patients who failed to achieve sustained virologic response after initial treatment with pegylated interferon and ribavirin (antiviral therapy nonresponders or relapsers) were enrolled; 1237 patients received maintenance therapy (Maintenance group) and 1201 received no treatment (Observation group).

Results: The pooled analyses found that patients in the Maintenance group had a significantly higher rate of normal alanine aminotransferase than did patients in the Observation group (pooled odds ratio [OR] 4.436, 95% confidence interval [CI] 1.225–16.064, $P = .023$), but there was no significant difference between the 2 groups in the incidence of hepatocellular carcinoma (pooled OR 0.872, 95% CI 0.501–1.519, $P = .630$), or the mortality rate (pooled OR 1.564, 95% CI 0.807–3.032, $P = .185$).

Conclusions: Interferon-based maintenance therapy in patients with chronic hepatitis C who failed initial antiviral therapy improved liver inflammation as indicated by blood chemistry (alanine aminotransferase).

Abbreviations: ALT = alanine aminotransferase, CHC = chronic hepatitis C, CIs = confidence intervals, DAA = direct-acting antivirals, HALT-C = hepatitis C antiviral long-term treatment against cirrhosis, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, I^2 = inconsistency index, OR = odds ratio, Peg-interferon = pegylated interferon, RCTs = randomized controlled trials, SVR = sustained virologic response.

Keywords: direct-acting antivirals, HALT-C, hepatitis C virus infection, peg-interferon

1. Introduction

The number of total global hepatitis C virus (HCV) infections has been estimated to be 80 (64–103) million.[1,2] Patients in China,

Pakistan, Nigeria, Egypt, India, and Russia together have accounted for more than half of total infections.[1,2] HCV infection causes 27% of cirrhosis and 25% of hepatocellular carcinoma cases worldwide.[3] When cirrhosis is established, the ultimate outcome is generally poor. The mortality associated with cirrhotic chronic hepatitis C (CHC) then is usually due to end-stage liver diseases including the development of liver decompensation or hepatocellular carcinoma (HCC).[4,5]

Before the introduction of protease inhibitors and direct-acting antivirals (DAAs) for treatment of CHC,[6,7] the standard treatment had been interferon-α and ribavirin.[8] The efficacy of interferon regimens is measured by their ability to achieve viral clearance with cessation of disease activity, referred to as the sustained virologic response (SVR). SVR is defined as the absence of detectable HCV-RNA in serum at indicated time points after the end of treatment. CHC patients in whom initial therapy fails to achieve SVR (interferon nonresponders or relapsers) become candidates for retreatment or long-term maintenance therapy. Koretz et al[4] stated in 2013 that some of these patients are not suitable candidates for ribavirin or protease inhibitors, but instead should be considered for retreatment with interferon alone.[4] Long-term interferon maintenance therapy usually consists of low-dose pegylated interferon (peg-interferon) given for 1 year or more.[4,9] With the recent availability of DAAs, the rates of SVR and virological cure have vastly increased in naive patients, and also in treatment-experienced patients.[7] However,

the controversy of DAA treatment-associated risk of HCC and altered type/pattern of HCC recurrence remains. Moreover, the high economic burden of DAA had prevented its use or reimbursement by the health authorities in some parts of the world. Therefore, interferon-based regimens are still a viable approach, especially in countries where the DAAs are not available or affordable.

Our hypothesis is that continuing peg-interferon therapy long-term as maintenance therapy reduces the risk of HCC and mortality in patients with CHC who failed initial antiviral therapy.

2. Materials and methods

2.1. Search strategy

PubMed, Cochrane, and Embase were searched in July, 2017, using combinations of the following search terms: "chronic hepatitis C," "liver cirrhosis," "liver fibrosis," "maintenance," "retreatment," "interferon," and "antiviral."

2.2. Selection of studies
2.2.1. Inclusion criteria. The included studies were: randomized controlled trials (RCTs) or 2-armed prospective studies of CHC; studies that enrolled patients who did not achieve a SVR after an initial treatment with interferon or interferon and ribavirin (nonresponders), or patients who relapsed after the end of the initial treatment (relapsers); studies of patients who received maintenance therapy with interferon (Maintenance group) versus control without further therapy (Observation group); and studies that had quantitative outcomes.

2.2.2. Exclusion criteria. Excluded studies were: retrospective studies, reviews, letters, comments, editorials, or case reports; studies that included patients with human immunodeficiency virus coinfection; studies that included patients who had SVR after the initial treatment; studies that compared interferon of different dosages or types, or compared interferon with other antiviral agents; and studies that had no quantitative outcome.

To identify studies that were eligible for the meta-analysis, the citations were screened by a 2-step process. First, the title and abstract of each article were examined, and citations not meeting the inclusion criteria or meeting the exclusion criteria were discarded. Second, full-text copies of the remaining citations were obtained and examined to identify those who met all the inclusion criteria and none of the exclusion criteria. Two independent reviewers identified eligible studies by using the search strategy described above. If any uncertainties regarding eligibility existed, a third reviewer was consulted. The reference lists of the relevant studies were hand-searched to identify other studies that met the inclusion criteria.

2.3. Data extraction

Data as in patient demographics (number of patients, treatment regimen, age, sex, and follow-up duration) and post-treatment outcomes (rate of normal alanine aminotransferase [ALT], incidence of HCC, and incidence of death) were extracted. Two independent reviewers extracted the data from eligible studies. A third reviewer was consulted for resolution of disagreement. Patient raw data or private information were not used or extracted during this process, and thus an ethics review by the institutional review board was exempt.

2.4. Data analysis

Odds ratio (OR) with 95% confidence intervals (CIs) were calculated between patients in Maintenance group and Observation group for each included study and for all studies combined. A chi-square-based test of homogeneity was performed, and the inconsistency index (I^2) and Q statistics were determined. Heterogeneity was determined by use of the I^2 statistic, which is defined as: 0% to 24%, no heterogeneity; 25% to 49%, moderate heterogeneity; 50% to 74%, large heterogeneity; and 75% to 100%, extreme heterogeneity. As the number of studies included in the meta-analysis was small, heterogeneity tests may have low statistical power. In case of under-powered heterogeneity tests, random-effects models are routinely used.[10] The National Research Council report recommends using random-effects approaches for meta-analysis and the exploration of sources of variation in study results.[11] Pooled effects were calculated, and a 2-sided P value <.05 was considered to indicate statistical significance.

Sensitivity analysis was carried out with the leave-one-out approach to investigate the validity and robustness of the results. The leave-one-out approach performs meta-analyses on each subset of the studies obtained by leaving out exactly 1 study once at a time. Publication bias, using a funnel plot, was not performed as >10 studies are needed for this type of analysis.[12] All analyses were performed with Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

2.5. Quality assessment

The quality of included studies were assessed by use of the Cochrane "assessing risk of bias" table as exemplified in the Cochrane Collaboration guidelines.[13] The table has 6 assessment items, which are: random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting risk.

3. Results

3.1. Literature search

The flow chart for study selection is illustrated in Fig. 1.

3.2. Study characteristics

Ten studies underwent full-text review. Four were excluded. Six RCTs met the eligibility criteria and were included in this meta-analysis. In total, the 6 RCTs enrolled 2438 chronic hepatitis C patients who failed to achieve SVR after an initial treatment with peg-interferon and ribavirin (antiviral therapy nonresponders) or relapsed (relapsers). Among the 2438 patients, 1237 received maintenance therapy (Maintenance group) and 1201 received no treatment (Observation group) in the maintenance therapy phase. The patient demographics, study design, and maintenance treatment protocols of the studies included in the meta-analysis are summarized in Table 1. The average age of patients was 45 to 52 years, and the majority of patients were men.

3.3. Meta-analysis

Four of the RCTs in the meta-analysis[14–17] provided the rates of normal serum ALT at follow-up. These studies had extreme heterogeneity (Q-statistic = 14.330, I^2 = 79.07%). The pooled
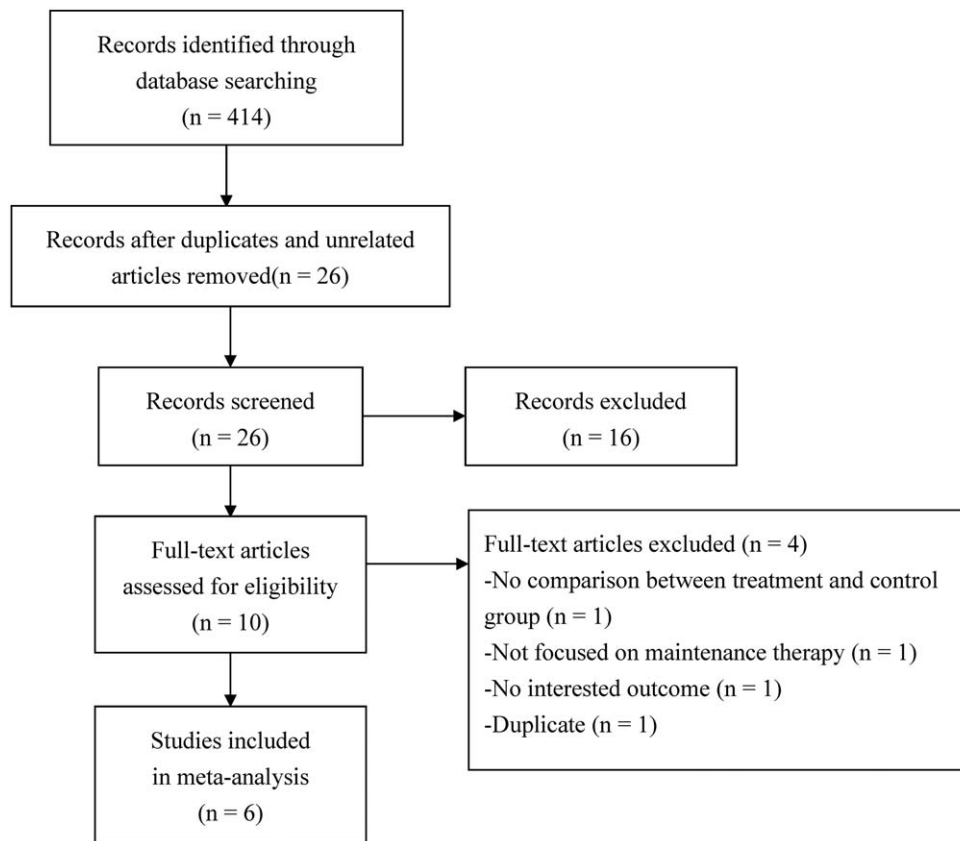
Figure 1. Flow diagram of study selection.

Table 1

Patient demographics and characteristics and maintenance protocols of the selected studies.

First author (y)	Study design	No. of patients	Groups	Maintenance treatment protocol	Averageage (y)	Male (%)	Duration of follow-up (y)
Poynard (2013)	RCT	270	Maintenance	Peg-IFNα-2b, 0.5 μg/kg/wk, for 2.3 y	49.8	72%	3.6
		270	Observation		49.2	70%	3.9
Bruix (2011)	RCT	311	Maintenance	Peg-IFNα-2b, 0.5 μg/kg/wk, for a maximum period of 5 y	52.3	66%	5
		315	Observation		52	68%	
DiBisceglie (2008)	RCT	517	Maintenance	Peg-IFNα-2a, 90 μg/wk for 3.5 y	51.1	70%	3.5
		533	Observation		50.1	73%	
Alric (2001)	RCT	29	Maintenance	Gradual tapering of IFN dose during 12 mos: 2 M IU 3 times weekly for 3 mos,1 M IU 3 times weekly for 3 mos, 1 M IU twice a wk for 3 mos, and 1 M IU once a wk for the last 3 mos	46.3	45%	2.5
		28					
			Observation		45.8	43%	
Shiffman (2009)	RCT	26	Maintenance	IFN-α-2b, 3M IU 3 times weekly for 24 mos	47.8	58%	2
		27	Observation		48.8	52%	
Bresci (1995)	RCT	28	Maintenance	Recombinant IFN-α, 3 M IU thrice weekly for 6 mos	47	64%	0.5
		28		Recombinant IFN-α, 6 M IU thrice weekly for 6 mos	48	57%	
		28		lymphoblastoid-IFN, 3 M IU thrice weekly for 6 mos	45	61%	
		28	Observation		46	54%	

IFN = interferon, IU = international unit, M = million, peg-IFN = pegylated interferon, RCT = randomized controlled trial.

Panel A

Study name	Event of normal ALT at follow-up		Statistics for each study					OR and 95% CI
	Maintenance	Observation	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Di Bisceglie (2008)	181 / 517	139 / 533	1.527	1.172	1.990	3.135	0.002	
Alric (2001)	20 / 29	2/28	28.889	5.608	148.826	4.021	<0.001	
Shiffman (2009)	16 / 26	11/27	2.327	0.773	7.003	1.503	0.133	
Bresci (1995)	15 / 84	0 / 28	12.712	0.736	219.701	1.749	0.080	
Overall			4.436	1.225	16.064	2.269	0.023	

OR and 95% CI scale: 0.01   0.1   1   10   100

Favors Observation Group   Favors Maintenance Group

Test for heterogeneity

$Q = 14.330$, $P = 0.002$, $I^2 = 79.07\%$

A

Panel B

Study name	HCC incidence		Statistics for each study					OR and 95% CI
	Maintenance	Observation	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Bruix (2011)	12 / 311	13 / 315	0.932	0.419	2.076	-0.171	0.864	
Di Bisceglie (2008)	12 / 517	15 / 533	0.821	0.380	1.770	-0.504	0.614	
Overall			0.872	0.501	1.519	-0.482	0.630	

OR and 95% CI scale: 0.1   0.2   0.5   1   2   5   10

Favors Maintenance Group   Favors Observation Group

Test for heterogeneity

$Q = 0.051$, $P = 0.822$, $I^2 = 0\%$

B

Panel C

Study name	Mortality		Statistics for each study					OR and 95% CI
	Maintenance	Observation	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Poynard (2013)	3 / 270	1 / 270	3.022	0.312	29.241	0.955	0.339	
Bruix (2011)	7 / 311	6 / 315	1.186	0.394	3.569	0.303	0.762	
Di Bisceglie (2008)	13 / 517	8 / 533	1.693	0.696	4.119	1.160	0.246	
Overall			1.564	0.807	3.032	1.324	0.185	

OR and 95% CI scale: 0.01   0.1   1   10   100

Favors Maintenance Group   Favors Observation Group

Test for heterogeneity

$Q = 0.597$, $P = 0.742$, $I^2 = 0\%$

Abbreviations: ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; OR, odds ratio; CI, confidence interval
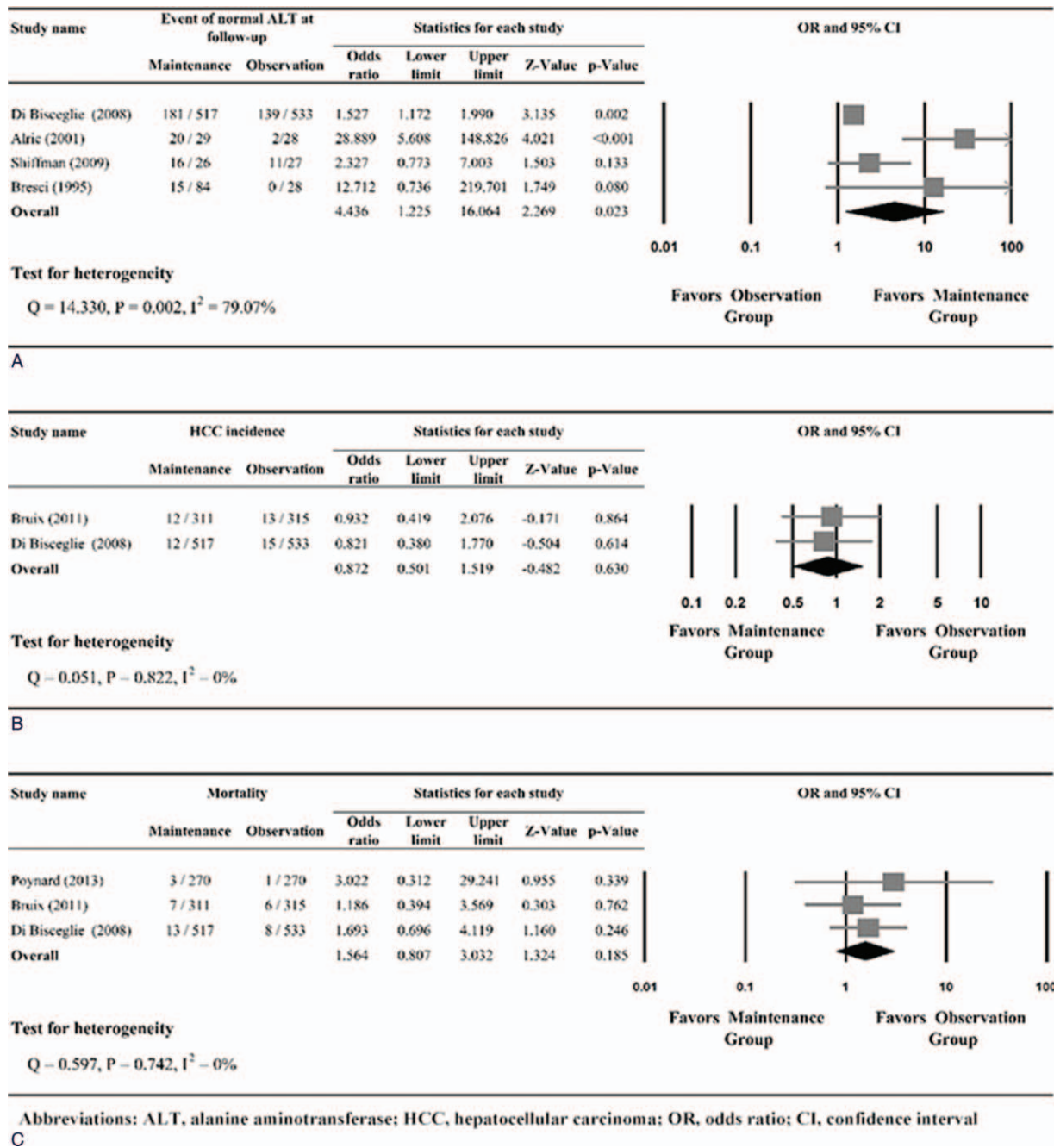
C

Figure 2. Forest plots illustrating the effect of maintenance therapy on the rate of (A) normal ALT, (B) HCC, and (C) mortality. ALT=alanine aminotransferase, HCC=hepatocellular carcinoma.

analysis found that patients in Maintenance group had significantly higher rate of normal ALT than did patients in Observation group (pooled OR 4.436, 95% CI 1.225–16.064, P=.023) (Fig. 2A).

Only 2 of the RCTs in the meta-analysis[14,18] provided the incidence rates of HCC. No heterogeneity was observed in the 2 studies (Q-statistic=0.051, I^2=0%). The pooled analysis found that there was no significant difference in the incidence of HCC between patients in Maintenance group and Observation group (pooled OR 0.872, 95% CI 0.501–1.519, P=.630) (Fig. 2B).

Three of the RCTs provided data on mortality.[14,18,19] There was no heterogeneity among these studies (Q-statistic=0.597,

I^2=0%). The pooled analysis found no significant difference in the mortality rate among patients in Maintenance group and Observation group (pooled OR 1.564, 95% CI 0.807–3.032, P=.185) (Fig. 2C).

3.4. Sensitivity analysis

Sensitivity analyses were performed by the leave-one-out approach, in which the meta-analysis was performed with each study removed in turn (Table 2). The direction and magnitude of combined estimates of neither HCC incidence nor mortality varied significantly upon removal of the studies, indicating that

Sensitivity analysis of selected studies.

First author (y)	Statistics with study removed				
	OR	Lower limit	Upper limit	Z	P
Normal ALT at follow-up					
DiBisceglie (2008)	8.325	1.344	51.588	2.277	.023
Alric (2001)	1.793	1.030	3.122	2.065	.039
Shiffman (2009)	7.038	0.729	67.980	1.686	.092
Bresci (1995)	3.795	0.949	15.176	1.886	.059
HCC incidence					
Bruix (2011)	0.821	0.380	1.770	−0.504	.614
Di Bisceglie (2008)	0.932	0.419	2.076	−0.171	.864
Mortality					
Poynard (2013)	1.471	0.736	2.939	1.093	.274
Bruix (2011)	1.828	0.799	4.184	1.429	.153
Di Bisceglie (2008)	1.418	0.526	3.820	0.690	.490

ALT = alanine aminotransferase, HCC = hepatocellular carcinoma, OR = odds ratio.

the meta-analysis had good validity and robustness, and the data were not overly influenced by each study. Pooled OR of normal ALT at follow-up remained >1 after each study was removed in turn, despite after the removals of 2 individual studies,[16,17] the OR became borderline significant, indicating no obvious influence of any individual study on the pooled estimate.

3.5. Quality assessment

Quality assessment of the studies is illustrated in Fig. 3. The quality of included studies was moderate. The most significant risk of bias came from performance bias (blinding of participants and personnel) because Observation group received no placebo drugs as described in studies by Bruix et al[18] and Poynard et al[19]; meanwhile, the other 4 studies did not give information about the concealment of treatment.

4. Discussion

The key findings of this meta-analysis were that interferon maintenance therapy improved the rate of normal serum ALT compared with the control group,[14–17] but there was no difference in mortality or incidence of HCC between the 2 groups. These results are consistent with those reported by Koretz et al,[4] published in Cochrane Database Systematic Review. Koretz et al included RCTs comparing interferon versus placebo or no treatment in CHC nonresponders and relapsers to previous interferon treatment with severe hepatic fibrosis. Based on all 7 trials, no significant difference was found in all-cause mortality, hepatic mortality, or incidence of HCC. In 2 combined trials in the meta-analysis with low risk of bias, the all-cause mortality was significantly higher in the interferon-treated patients. Similar findings have been reported by Di Bisceglie et al,[20] who concluded that long-term maintenance peg-interferon in patients with advanced CHC is associated with an excess overall mortality, primarily due to nonliver-related causes among patients with bridging fibrosis. In the Koretz et al's[4] study, serum ALT values, which can reflect hepatic damage, were not analyzed, but histologic evidence of inflammation was improved by interferon treatment.

Only 2 studies[14,18] in the present meta-analysis reported HCC incidence, and found that maintenance therapy with interferon did not prove to be beneficial. This is in line with that reported by Lok et al,[21] who extended the duration of follow-up of the hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) trial[14] and found that long-term low-dose peg-interferon therapy did not reduce the incidence of HCC among patients with advanced hepatitis C who did not achieve SVRs. Thus, the hope to adopt maintenance interferon therapy to reduce the chances of HCC developing in CHC patients who failed initial treatment has not been fulfilled.

An inevitable impression of using interferon as a therapy for CHC is the drug's frequent and troubling side effects, including fatigue, headache, chills/rigors, fever, musculoskeletal pain, and weight loss. In the systematic review by Koretz et al,[4] the authors noted an increase in adverse effects and a significantly worse pain score in interferon-treated patients compared with placebo-treated patients or untreated patients. Partly because of these side effects, interferon-based regimens are poorly tolerated. Steffen et al[22] have stated that patients with higher motivation and compliance should be considered for maintenance interferon therapy of CHC.

Dose adjustment of interferon may ameliorate the side effects associated with the drug, and indeed an extended low-dose interferon trial performed by Tarantino et al[23] has shown to increase SVR rates in patients with prior complete response at the end of standard treatment. However, the HALT-C trial found that low-dose peg-interferon therapy was still associated with worsening of health-related quality of life, symptoms, and male patients' sexual health, despite that cognitive function and depression were less affected.[24–26] Furthermore, lower doses of interferon were used in several studies included for analysis in this report,[14,15,18,19] but the efficacy findings were not altered in the sensitivity test where individual studies were taken out. This implies to that dose of interferon plays a minor role in the efficacy of interferon-based maintenance therapy in nonresponders/relapsers.

We acknowledge that this meta-analysis has limitations. First, only 6 RCTs were included. Second, the number of patients is small in 3 of the included studies (54–56 patients each).[15–17] Third, scoring systems for evaluating fibrosis, definition of nonresponder, and therapy before maintenance treatment varied among studies. Fourth, a partial overlap of patient populations among 2 studies may have occurred: Poynard et al[19] included adult patients with CHC infection and biopsy-confirmed moderate to severe fibrosis from EPIC,[3] and Bruix et al[18] included all patients who had compensated biopsy-proven cirrhosis (Child-Pugh class A) from EPIC.[3]
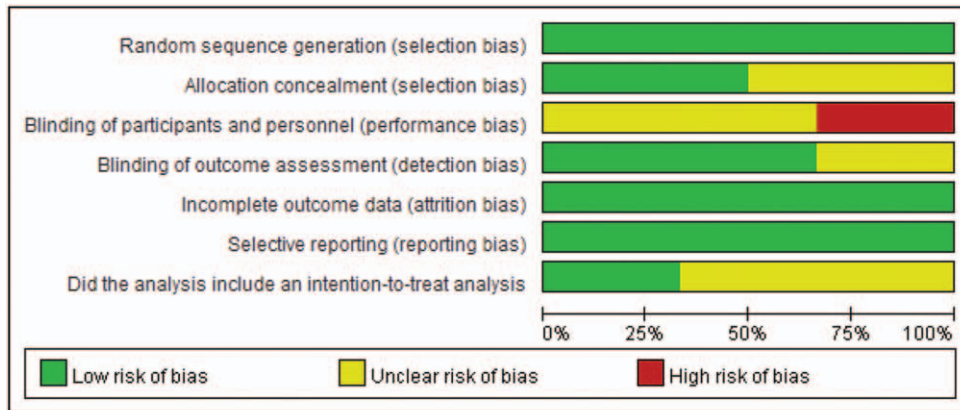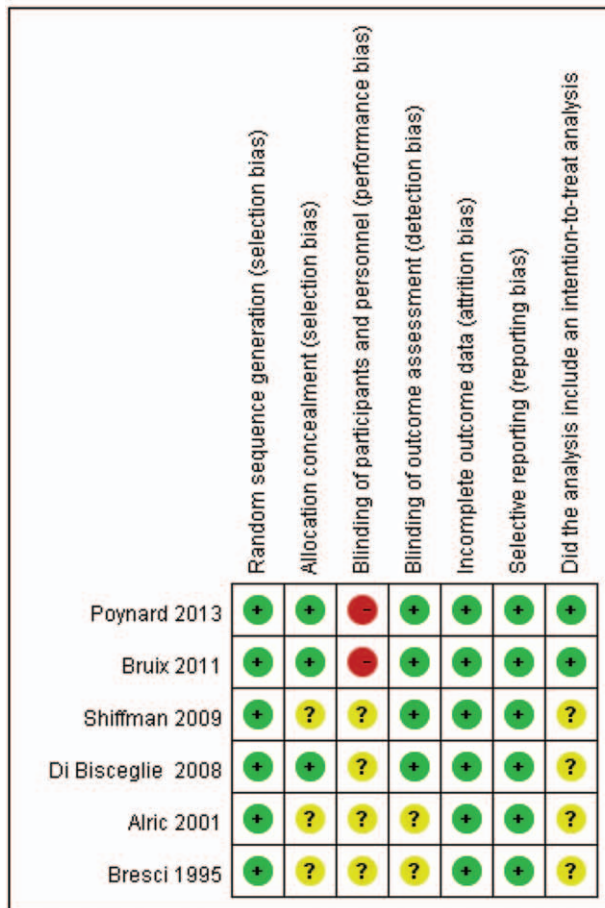
Figure 3. Quality assessment. (A) Summary of bias of the included studies. (B) Risk of bias for each included study.

Shiffman[27] wrote in 2010 that "Based upon the available data, there appears to be no rationale for utilizing PEG-IFN maintenance therapy in patients with cirrhosis, and this approach does not reduce the risk of HCC." Regrettably, research in the ensuing years has yielded little grounds for reversal of this opinion. Major outcome variables in patients treated with long-term interferon products have not been improved, although modest positive responses have been observed in ALT improvements,[14–17] attaining

SVR at a significant but low (22%) rate,[28] reducing progression of fibrosis,[19] and improving disease activity scores.[19]

In the DAA era that we currently stand,[7] better options than interferon-based regimens are available for treating CHC. Interferon-based maintenance for CHC may still be considered in clinical settings where DAAs are unavailable or unaffordable, but as Heim[29] wrote in 2013, the interferon epoch is coming to an end.

5. Conclusions

This meta-analysis found that interferon-based maintenance therapy of CHC may improve ALT, a biochemical indicator of liver inflammation. However, similar to previous studies, this maintenance therapy did not reduce the incidence of HCC or mortality. Further study of this therapy seems unlikely to yield a significantly different view or clinically meaningful results.

Author contributions

Conceptualization: Yuan-Ti Lee.
Data curation: Hung-Chang Hung, Shih-Ming Tsao.
Formal analysis: Hsien-Hua Liao, Shiuan-Chih Chen, Shih-Ming Tsao.
Investigation: Hung-Chang Hung.
Writing – original draft: Hung-Chang Hung, Hsien-Hua Liao, Shiuan-Chih Chen, Shih-Ming Tsao, Yuan-Ti Lee.
Writing – review & editing: Yuan-Ti Lee.

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