International Journal of Technology Assessment in Health Care, **25:1** (2009), 56–62.

doi:10.1017/S0266462309090084

Pegylated and non-pegylated interferon-alfa and ribavirin for the treatment of mild chronic hepatitis C: A systematic review and meta-analysis

Debbie Hartwell, Jonathan Shepherd
University of Southampton

Objectives: Traditionally, patients with chronic hepatitis C virus (HCV) infection have not received treatment until their infection reaches the moderate to severe stage. The aim of this systematic review was to assess the clinical effectiveness of pegylated (PEG) and non-pegylated interferon (IFN) alfa and ribavirin (RBV) for the treatment of adults with histologically mild HCV.
Methods: We performed a sensitive search of fourteen electronic bibliographic databases for literature that met criteria defined in a research protocol. Two reviewers independently selected studies, extracted data and assessed methodological quality.
Results: Ten randomized, controlled trials (RCTs) were included. Treatment with PEG + RBV combination therapy resulted in significantly higher sustained virological response (SVR) rates than treatment with IFN + RBV combination therapy. Treatment for 48 weeks with PEG + RBV was significantly more effective than the same treatment for 24 weeks. Significantly higher SVR rates were seen with IFN + RBV compared with either IFN monotherapy or no treatment. In the meta-analysis (four IFN trials), the relative risk of not experiencing an SVR was 0.59 (95 percent CI, 0.51 – 0.69) and was statistically significant ($p < .00001$). SVRs were higher for patients with genotype non-1 compared with genotype 1 for both PEG + RBV and IFN + RBV treatments.
Conclusions: Patients with histologically mild HCV can be successfully treated with both PEG and IFN combination therapy, and response rates are broadly comparable with those achieved in patients with advanced disease. Treating patients in the early milder stages of HCV is, therefore, a clinically effective option.

Keywords: Mild hepatitis C, Pegylated interferon-alfa, Non-pegylated interferon-alfa, Ribavirin, Systematic review

The authors acknowledge Jeremy Jones, Peter Davidson, Alison Price, and Norman Waugh, who were all involved in the original health technology assessment report. Thanks are also due to the HTA UK mild HCV trial team for access to their publications, and in particular Professor Howard Thomas for professional advice in the original health technology assessment report. D.H. and J.S. contributed to the development of the protocol, inclusion screening, data extraction/critical appraisal, writing of the original health technology assessment report, drafting of the article, critical revision of the article for intellectual content, and final approval of the article. This project was completed as part of an update review funded by the NIHR Health Technology Assessment Programme (project no. 04/49/01) and commissioned on behalf of the National Institute for Health and Clinical Excellence (NICE). It has been published in full in *Health Technology Assessment* 2007, Vol. 11, No. 11. See the HTA Programme Web site (www.hta.ac.uk) for further project information. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health. No ethics approval are required.

Hepatitis C is a blood borne viral infection that is commonly transmitted by use of contaminated hypodermic needles and infected blood or blood products. It is estimated that approximately 170 million people worldwide may be chronically infected with the hepatitis C virus (HCV), with a prevalence of around 250,000 to 400,000 for the UK (5) and more than 2.7 million for the United States (21). It is difficult to estimate the proportion of infections which could be considered as being mild because this currently requires verification by a liver biopsy. Studies vary in their estimations of the proportion of mild HCV infections. In one cohort, the estimate was as high as 85 percent (18). In the early stages of HCV infection, symptoms are generally mild. However, there may be a significant reduction in patients' quality of life, with common symptoms including fatigue, malaise, depression, headache, bodily pain, and cognitive impairment (6). HCV infection is a slowly progressive inflammatory liver disease which can result in cirrhosis, hepatocellular carcinoma and, in the absence of successful liver transplant, death. Disease progression is variable, and around 30 percent of carriers will develop liver cirrhosis within 20 years.

There are six major genotypes and several sub-types of HCV, the prevalence of which varies geographically. In England and Wales, the most prevalent genotypes are 3a (37 percent), 1a (32 percent), and 1b (15 percent). Genotype 2a is common in Japan and China, whilst 2b is prevalent in the United States and northern Europe. Genotypes 4 and 5 are most common in Africa, including Egypt, and the Middle East, and genotype 6 predominates in Southeast Asia. Type 3 is most common in injecting drug users (8;12), and type 1 in patients with hemophilia, infected by means of contaminated blood products (12). Genotype is a key predictor of the effectiveness of anti-viral treatment, and patients with genotypes 2 and 3 generally respond better to treatment than genotypes 1, 4, 5, and 6.

The first licensed treatment for HCV was the immunomodulatory drug interferon-alfa (IFN). This was associated with response rates of up to 20 percent (15), boosted to around 40 percent with the addition of the anti-viral drug ribavirin (RBV) licensed in the late 1990s (16). A longer-acting pegylated form of IFN was later introduced which, in combination with RBV, increased SVRs to between 50 percent to 60 percent (19).

Traditionally, patients have not received anti-viral treatment until their liver pathology reaches the moderate to severe stage. However, if effective, treatment during the mild stage may be beneficial in improving health-related quality of life and may also reduce the likelihood of onward transmission of infection. It is, therefore, necessary to assess the clinical effectiveness of anti-viral treatment in this patient group.

METHODS

Searches

We performed a sensitive literature search up to April 2007 of fourteen electronic databases including the Cochrane library, Medline, Embase, DARE (Database of Abstracts of Reviews of Effectiveness), and the HTA database (Health Technology Assessment). We also screened bibliographies of retrieved papers for additional citations, searched eleven relevant Web sites (e.g., British Liver Trust) for completed or on-going studies, consulted experts, and searched manufacturer and sponsor submissions to the National Institute for Health and Clinical Excellence (NICE). All searches were limited to English language only.

Inclusion Criteria and Study Selection

A peer-reviewed, published protocol specified the inclusion criteria. We included RCTs or systematic reviews of RCTs. Studies had to report an evaluation of PEG 2a or 2b either as dual therapy with RBV, or monotherapy for those unable to tolerate RBV. Studies of IFN 2a or 2b with RBV were also eligible. We included studies comparing the different drugs with placebo, each other, or best supportive care. Only studies reporting $\geq$70 percent of adult patients at baseline with histologically mild HCV were eligible. Outcomes included virological response at the end of treatment, and sustained clearance of infection as shown by absence of viral RNA six months or longer after the end of treatment (sustained viral response – SVR). Other outcomes included biochemical response, histological response, adverse events, and health-related quality of life. Studies were excluded if they did not meet the inclusion criteria or if it was impossible to determine the severity of HCV in the patient group. One reviewer screened the titles and abstracts of all identified studies, and a second reviewer checked a random sample of these. On retrieving full text versions of relevant papers, two reviewers independently applied an inclusion worksheet to identify appropriate trials.

Data Extraction Strategy

We independently abstracted data from all studies using a standardized form. Data were abstracted on study design, population, and severity of HCV, intervention and the outcome variables listed above. For each study, the extraction of data and application of methodological quality criteria (14) were undertaken by one reviewer and checked by a second, with any disagreements resolved through discussion.

Data Synthesis

The trials were reviewed in a narrative synthesis with the main results described qualitatively and tabulated. Quantitative meta-analysis was only possible for the comparison of IFN + RBV with IFN ($n = 4$ RCTs). Sustained virological

response rates were pooled as a dichotomous variable, expressed as relative risks (RR) with 95 percent confidence intervals. The data analysis was performed using a fixed-effects model using meta-analysis software (RevMan 4.2.8, Cochrane Collaboration, Oxford). Statistical heterogeneity between trials was tested with Chi-squared tests, whereby $p \leq .1$ indicates significant heterogeneity, and quantified using the I^2 statistic, whereby a value of 25 percent is considered low, 50 percent moderate, and 75 percent high (14). Data were analyzed on an intention to treat basis. In all other comparisons meta-analysis was not possible as only one RCT was available or relevant outcome data were not reported.

Further details on the search strategy and the systematic methods used to inform the review are presented in the full research report (20). The results presented here are an update of this report incorporating more recent searches and inclusion of relevant data.

RESULTS

Quantity and Quality of Research

We identified 4,321 references to studies of the clinical effectiveness of treatments for HCV. After screening the titles and (where available) abstracts, 790 full papers were screened for potential inclusion. Of these 790, 10 were RCTs of anti-viral treatment in patients with histologically mild HCV, and were included. Four of these ten studies were included in a meta-analysis (see Figure 1 for further detail of the number of studies included and excluded at each stage) (11).

Study characteristics are presented in Supplementary Table 1 (available at www.journals.cambridge.org/thc). Of the 10 RCTs (3;4;7;9;10;17;22–25), four evaluated PEG 2a in combination with RBV (4;7;23;25). Three of these compared different regimens of PEG + RBV (7;23;25), whereas the fourth compared PEG + RBV with IFN + RBV (4). The remaining six RCTs evaluated IFN in combination with RBV, compared with a different regimen of IFN + RBV, (9) IFN monotherapy (3;10;17;22) or no treatment (24). A total of 2,776 patients were randomized worldwide and all the trials were based on middle-aged (mean age range, 36–49 years), adult patients. The majority of trials included patients who were treatment naïve ($n = 2{,}724$) and without comorbidities (e.g., hemophilia). Only one study included patients who were co-infected with HCV and HIV (4). Treatment lasted from 16 to 48 weeks, and follow-up was 24 weeks after treatment ceased. In general, the RCTs were of good methodological quality, although reporting of randomization methods and blinding of assessors was generally poor (Supplementary Table 2). A total of 460 participants were enrolled in the four trials included in the meta-analysis comparing IFN + RBV with IFN monotherapy (10) or IFN + placebo (3;17;22).

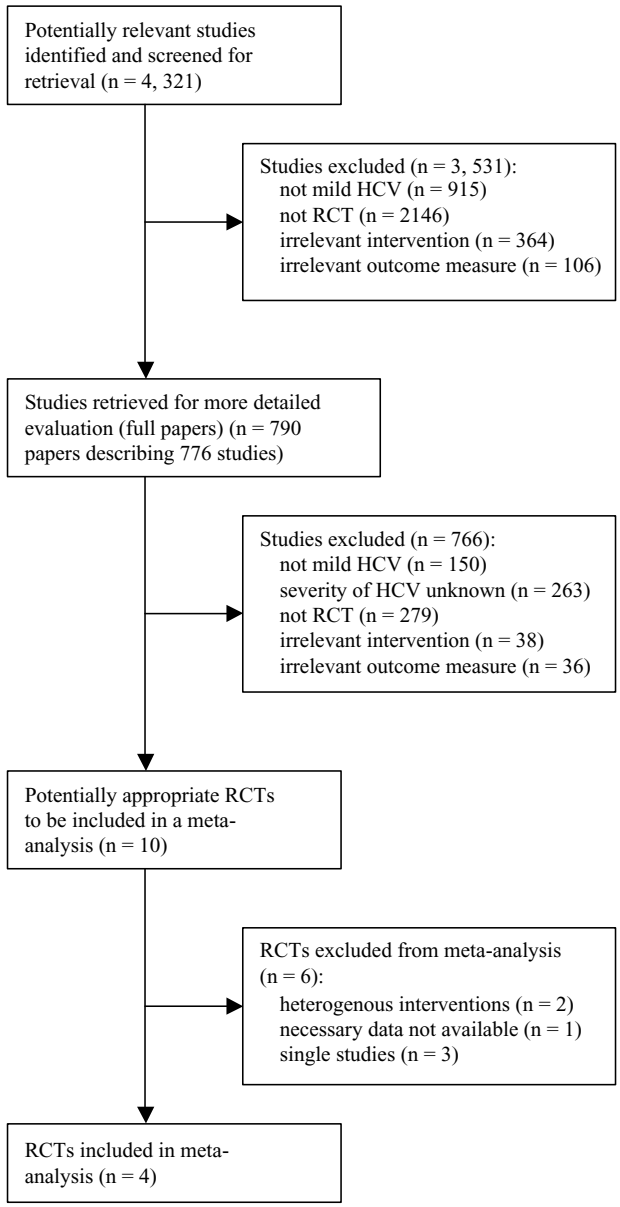

Figure 1. The QUOROM flow diagram (11). HCV, hepatitis C virus; RCT, randomized, controlled trial.

Sustained Virological Response

Table 1 reports SVRs for two of the four PEG trials. In the trial by Zeuzem and colleagues (25), treatment for 48 weeks with PEG + RBV was significantly more effective than the same treatment for 24 weeks (SVR 52 percent versus 30 percent; $p < .001$), with a relative risk of 1.7 (95 percent CI, 1.4 – 2.2). No patient in the untreated control group had an SVR. In the trial by Chung and colleagues (4), treatment with PEG + RBV for 48 weeks resulted in a significantly higher SVR than treatment with IFN + RBV for 48 weeks (SVR 27 percent versus 12 percent; $p = .03$). In the other two PEG studies (7;23), SVRs were only reported according to

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Table 1. Sustained Virological Response (PEG Trials)

Study Outcome: SVR at follow-up	Treatment arms				
Zeuzem et al., 2004 (25) Multicenter, open-label RCT	PEG α-2a (180 μg) + RBV (800 mg), 24 wk (n = 212)	PEG α-2a (180 μg) + RBV (800 mg), 48 wk (n = 210)	No treatment (n = 69)	Risk diff (95% CI)	RR, 48 vs 24 wk (95% CI), p value[a]
% with response (95% CI)	30% (24 – 36)	52% (45 – 59)	0	22 (13 – 31)	1.7 (1.4 – 2.2), $p < .001$
Chung, 2004 (4) Multicenter RCT HIV/CHC co-infected patients	PEG α-2a (180μg) + RBV (600–1,000 mg) 48 wk (n = 66)	IFN α-2a (3–6 MU) + RBV (600–1,000 mg) 48 wk (n = 67)	p value[a]		
% with response (n/N)	27% (18/66)	12% (8/67)	$p = .03$		

[a]Between-group comparison.
RR, relative risk; PEG, pegylated interferon-alfa; SVR, sustained virological response; RCT, randomized, controlled trial; RBV, ribavirin; CHC, chronic hepatitis C.

Table 2. Sustained Virological Response (IFN Trials)

Study Outcome: SVR at follow-up	Treatment arms		
Cheng, 2002 (3) Double-blind RCT	IFN α-2b (6 MU) + RBV (1,000–1,200 mg), 24 wk (n = 26)	IFN α-2b (6 MU) + placebo, 24 wk (n = 26)	p value[a]
% with response (n/N)	69% (18/26)	23% (6/26)	<.001
Kim, 2005 (9) Single-center, open-label RCT	IFN α-2a (9MU) + RBV (1,000 mg), 24 wk (n = 30)	IFN α-2a (10 MU, 1 wk then 9 MU, 23 wk) + RBV (1,000 mg), 24 wk (n = 29)	p value[a]
% with response (n/N)	53% (16/30)	59% (17/29)	0.88
Mangia, 2001 (10) Multicenter, open-label RCT	IFN α-2b (5 MU) + RBV (1,000–1,200 mg), 48 wk (n = 96)	IFN α-2b (5 MU), 48 wk (n = 96)	p value[†]
% with response (95% CI)	54% (44–64)	21% (13–29)	.0001
Reichard, 1998 (17) Multicenter, double-blind RCT	IFN α-2b (3 MU) + RBV (1,000–1,200mg), 24 wk (n = 50)	IFN α-2b (3 MU) + placebo, 24 wk (n = 50)	p value[†]
% with response (n/N)	42% (21/50)	20% (10/50)	.03
Verbaan, 2002 (22) Multicenter, double-blind RCT	IFN α-2b (3 MU) + RBV (1,000–1,200 mg), 52 wk (n = 57)	IFN α-2b (3 MU) + placebo, 52 wk (n = 59)	p value[†]
% with response (n/N)[a]	54% (31/57)	20% (12/59)	<.001
Wright, 2005 (24) Multicenter, open-label RCT	IFN α-2b (3 MU) + RBV (1,000–1,200 mg), 48 wk (n = 98)	No treatment (n = 98)	p value[a]
% with response (n/N)	33% (32/98)	0 (0/98)	≤.00001

[a]Between-group comparison; [a]HCV RNA tested in 99 patients at follow-up (sera from 17 patients were missing).

genotype (Supplementary Table 3). However, Hadziyannis and colleagues (7) reported that PEG + RBV (standard dose 1,000–1,200 mg per day) for 48 weeks produced an overall SVR of 63 percent (95 percent CI, 59 – 68). In addition, patients treated for 48 weeks were more likely to achieve an SVR compared with patients treated for 24 weeks for both standard dose and low dose RBV (OR 1.53 (95 percent CI, 1.17 – 2.01); $p = .002$).

Five IFN trials (Table 2) reported significantly higher SVR rates with IFN + RBV (range, 33–69 percent) compared with either IFN monotherapy (range, 18–23 percent) or no treatment (zero response). In the sixth trial, SVR rates were not significantly different between patients receiving an initial high dose of IFN + RBV compared with conventional IFN + RBV dosing (9). When four of the IFN trials were meta-analyzed, the relative risk (RR) of not experiencing an SVR was 0.59 (95 percent CI, 0.51 – 0.69) and was statistically significant ($p < .00001$) (Figure 2). Heterogeneity was not statistically significant ($p = .29$) and the I^2 value was 20.7 percent.

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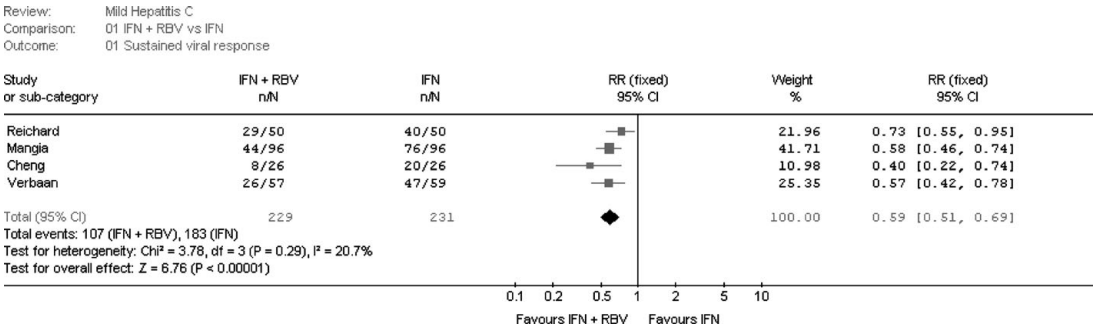

Figure 2. Forest plot for randomized, controlled trials (RCTs) of interferon-alfa plus ribavirin (IFN + RBV) versus IFN.

SVR by Genotype

SVR rates according to genotype were reported by all the included studies with broadly similar results. It should be noted that reporting of genotype groups was not consistent across trials making comparisons difficult, and few trials reported within-group comparisons. SVRs were higher for patients with the more favorable genotypes (i.e., genotypes 2 and 3, commonly labeled as "non-1") compared with genotype 1, irrespective of treatment (Supplementary Tables 3 and 4). In two of the PEG trials, between-group comparisons showed that patients with genotype 1 treated for 48 weeks had significantly higher response rates than patients on the same therapy for 24 weeks (7;25). In the trial by Hadziyannis and colleagues (7), this effect was shown by pooling together all patients with genotype 1 treated for 48 weeks compared with 24 weeks, yielding a statistically significant odds ratio (OR) in favor of 48 weeks treatment (OR 2.19, 95 percent CI, 1.52 – 3.16; $p < .0001$). Treatment duration did not have a significant effect on virologic response for patients with genotype 2 or 3 for either of these PEG trials.

Biochemical Response

One PEG (23) and four IFN trials (3;9;10;17) reported alanine aminotransferase (ALT) response rates after treatment (Supplementary Tables 5 and 6). Response was measured by reduction in ALT to normal levels. For the four IFN trials, response rates subsided between end of treatment and follow-up. Sustained biochemical response was greater for IFN + RBV compared with IFN monotherapy or IFN with placebo, reaching significance in two trials (3;10) and borderline significance in a third trial (17). The magnitude of response varied according to dose and regimen.

In the trial by Mangia and colleagues (10) the combined biochemical and virological response rate was more than 2.5 times higher ($p < .0001$) in patients receiving IFN + RBV compared with patients receiving IFN alone. At the end of follow-up, normalization of ALT values was associated with undetectable levels of serum HCV RNA in 71 of 72 patients (98.6 percent) who had an SVR. Serum HCV RNA levels remained detectable after treatment, despite persistently normal serum ALT concentration, in five of 77 patients (6.5 percent), of which three were combination therapy and two were IFN monotherapy.

Histological Response

Histological response rates were reported in five RCTs, (3;4;9;17;22) and are presented in Supplementary Tables 7 and 8. Only one of the PEG trials reported changes in liver histology. Chung and colleagues (4) report histological response for patients who achieved a virologic response at week 24, and for those who did not. Just over half the virologic responders who underwent a biopsy were classed as histologic improvers. Approximately one third of virologic nonresponders who underwent biopsy achieved a histologic response. There was no difference between treatment groups.

Four of the IFN trials reported changes in liver histology. There were no significant changes in fibrosis scores between groups in the three trials that reported this measure. For patients who experienced a sustained virological response in the trial by Verbaan and colleagues, (22) there was a significant improvement ($p \leq .018$) in mean inflammation grade score, irrespective of the treatment group. There was no significant change in nonresponders. Verbaan and colleagues also reported that the low fibrosis stage (mean stage 0.3 and 0.4 for IFN + RBV, and IFN + placebo groups respectively) did not change in either group, irrespective of treatment results, but data were not presented (22).

Quality of Life and Adverse Events

Data on health-related quality of life (HRQoL) was available for one IFN RCT (comparing IFN + RBV versus no treatment) (24), and one PEG RCT (comparing PEG + RBV for 24 weeks versus 48 weeks versus no treatment), the latter reported by Arora et al. (1), a more recent publication of HRQoL data from the Zeuzem et al. trial (25). Both trials used the validated Short Form-36 (SF-36), a generic health status survey of general health items. At 24 weeks after the end of treatment, HRQoL scores were significantly better in patients with an SVR compared with untreated patients for general health and vitality in the PEG trial (1), and

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additionally bodily pain in the IFN trial (24). The IFN trial also reported a significant improvement in the physical health component summary score in both SVR and non-SVR patients compared with controls ($p < .05$) (24).

The trials varied substantially in the detail of their reporting of premature withdrawal and adverse events. However, the most frequently occurring adverse events were the same in all ten RCTs, and included influenza-like symptoms such as headache, fatigue, fever, and myalgia. Depression also occurred quite commonly. Overall, the incidence of adverse events did not differ greatly between treatment groups for all the trials, with the exception of one (2;4) where subjects treated with PEG were more likely to have dose modifications compared with those treated with IFN. However, these were patients co-infected with HIV. In two trials, the incidence of adverse events was higher in the treatment groups compared with no treatment, as would be expected.

DISCUSSION

This systematic review has assessed the clinical effectiveness of anti-viral treatment in patients with mild HCV, a group previously not considered for therapy. The evidence base for antiviral treatment in this patient group is relatively smaller than that for treatment in patients with moderate to severe disease. Nevertheless, ten RCTs of patients with predominantly mild HCV were included in the review. Up to 63 percent of patients with histologically mild HCV treated with pegylated interferon-alfa and ribavirin achieve an SVR. Between 33 percent and 69 percent of mild HCV patients treated with non-pegylated interferon-alfa and ribavirin, the previous standard treatment, also respond (depending on variations in dose and regimen). These response rates are broadly comparable with those achieved in patients with advanced disease (54–61 percent) (19). Treating patients in the early milder stages of HCV, therefore, appears to be comparable in effectiveness as treating when liver disease has progressed. This is particularly so for patients with favorable genotypes 2 and 3 in whom the proportion successfully treated reached as high as 80 percent. Differences in virological response reported in this review might be explained by heterogeneity in the interventions and comparators between the trials.

The systematic review has some limitations. The evidence base for the effectiveness of antiviral treatment in mild HCV is much smaller than that for more advanced disease. Searches identified comparatively few RCTs of treating mild HCV patients, many of which were heterogeneous in interventions, comparators and methods, prohibiting a more comprehensive meta-analysis. Additionally, constructing a definition of mild HCV that could be used in the screening of potentially eligible studies was problematic. This was in part due to the use of different liver biopsy classification systems and their comparability, as well as failure to report baseline fibrosis scores of patients or not reporting which biopsy classification system was used. Furthermore, it was expected that very few trials were likely to recruit exclusively mild patients, and it was thus necessary to define a minimum threshold (70 percent) for the proportion of histologically mild patients in an eligible trial. It, therefore, has to be accepted that the SVRs reported by the included trials reflect treatment outcome for up to 30 percent of patients with moderate to severe HCV.

POLICY IMPLICATIONS

NICE have issued guidance to the health service in England and Wales recommending combination therapy (pegylated interferon-alfa and ribavirin) for the treatment of patients with mild HCV (13). This was based on the evidence from our full systematic review showing the clinical and cost effectiveness of treating patients with mild HCV (20), and is the first time that treatment in this patient group has been examined at a policy level. The emphasis is now on when to treat, rather than whether to treat, although given the nature of anti-viral treatment involving both oral and parenteral administration and some unpleasant side effects, not all patients will want to be treated, at least in the short term. The NICE guidance recommends that the decision on when to treat patients with mild HCV (i.e., immediately or when the disease has reached a moderate stage) should be discussed at an individual level between clinicians and patients. Decision makers will need to consider the cost and resource implications of extending treatment to a wider group. Other countries differ slightly in their practices of treating mild HCV patients. In the current American Association for the Study of Liver Diseases (AASLD) guidelines (21), treatment is indicated for patients with moderate-severe or severe HCV, whilst treatment for patients with mild HCV are considered on an individual basis.

Future research needs to be directed toward newer, potentially more effective interventions, particularly those that improve treatment response in patients with genotype 1, with minimal adverse effects.

CONTACT INFORMATION

Debbie Hartwell, PhD (d.hartwell@soton.ac.uk), Research Fellow, **Jonathan Shepherd**, MPhil (jps@soton.ac.uk), Principal Research Fellow, Southampton Health Technology Assessments Centre, Wessex Institute for Health Research and Development, University of Southampton, Mailpoint 728, Boldrewood, Southampton, SO16 7PX, UK

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