Evidence shows that a combination therapy of ribavirin plus interferon clears hepatitis C virus from the blood in about 40% of patients with chronic hepatitis C infection, but the effects on clinical outcomes are unclear. We evaluated the beneficial and harmful effects of ribavirin plus interferon vs interferon alone for treatment of patients with chronic hepatitis C infection. Randomized trials were included irrespective of blinding, language, or publication status. Trials were identified through the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Library, MEDLINE, EMBASE, manual searches of bibliographies and journals, and correspondence with experts (in May 2004). Data were extracted independently by 2 reviewers. The primary outcomes were morbidity plus mortality and viral clearance. Secondary outcomes included histologic response, quality of life, and adverse events. Previous antiviral therapy (treatment-naive patients, relapsers, or nonresponders), patient characteristics, treatment regimen, methodological quality, and duration of follow-up were extracted. We included 72 trials with a total of 9991 enrolled patients. Treatment with ribavirin plus interferon significantly reduced morbidity plus mortality (Peto odds ratio, 0.46; 95% confidence interval [CI], 0.22-0.96) and significantly improved sustained viral clearance in treatment-naive patients (risk ratio, 0.72; 95% CI, 0.68-0.76), relapsers (risk ratio, 0.63; 95% CI, 0.54-0.73), and nonresponders (risk ratio, 0.89; 95% CI, 0.84-0.94). Combination therapy also significantly improved liver histologic response. The effects on quality of life are unclear. However, combination therapy significantly increased the risk of hematological, dermatological, gastrointestinal, and several other types of adverse events. In conclusion, the effect of ribavirin plus interferon on viral clearance may lead to reduced mortality and morbidity in patients with chronic hepatitis C infection. However, combination therapy is associated with increased risk for adverse events.
likely to occur. Furthermore, it is probably unethical to conduct new long-term trials in which controls are randomized to a treatment presumably inferior to that currently recommended. Epidemiological studies (eg, comparing mortality or morbidity in patients with and without viral clearance) are possible, but the results may be biased. We performed an updated systematic review and meta-analysis of randomized trials on therapy with ribavirin plus interferon (combination therapy) vs interferon alone (monotherapy) for chronic hepatitis C infection; our focus was on clinical outcomes.

METHODS

LITERATURE SEARCH

Two of us (J.B. and L.L.G.) selected eligible trials using electronic searches of the Cochrane Hepato-Biliary Group Controlled Trials Register (May 2004), the Cochrane Library (Issue 1, 2004), MEDLINE (1966-May 2004), and EMBASE (1991-May 2004). The searches included the terms chronic hepatitis-C, ribavirin, interferon, and random. We identified additional trials through bibliographies in relevant articles and hand searches of specialist journals and conference proceedings. We asked authors of included trials and pharmaceutical companies for additional information about published or unpublished trials.

STUDY SELECTION

We included randomized trials on interferon plus ribavirin vs interferon alone for chronic hepatitis C infection irrespective of publication status or language. The type, dosage, and duration of treatment were not considered in the inclusion criteria but were evaluated in sensitivity analyses. Included patients could be treatment naive, relapers, or nonresponders to previous antiviral therapy. We excluded trials on patients with human immunodeficiency virus or trials on patients treated for hepatitis C during liver transplantation.

DATA EXTRACTION

Two reviewers (J.B. and L.L.G.) independently gathered data and assessed the methodological quality of included trials. The extracted patient characteristics included the mean age, percentage of men, percentage with cirrhosis, and percentage with genotype 1. Trial quality assessments included evaluations of randomization procedures and blinding. The intervention regimen and duration of follow-up were registered. We resolved disagreements through discussions before analyses and contacted primary investigators if data were not provided in the published trial reports. The 2 primary outcome measures were (1) the composite outcome of liver-related morbidity (development of cirrhosis, ascites, variceal bleedings, or hepatocellular carcinoma) plus all-cause mortality and (2) failure of clearance of the hepatitis C virus for at least 6 months (sustained virological response). Secondary outcomes included liver-related morbidity, all-cause mortality, histologic response, quality of life, and adverse events.

STATISTICAL ANALYSIS

We analyzed data by intention to treat and included all patients. We included patients irrespective of compliance or follow-up in an intention-to-treat analysis. Patients lost to follow-up were counted as nonresponders. In addition, we performed per-protocol analyses of histologic response. We performed random- and fixed-effects meta-analyses with 95% confidence intervals (CIs) for all outcomes using summary statistics from the included trials. Because we expected few events, we decided a priori to use Peto odds ratios (ORs) for analysis of morbidity plus mortality. The remaining outcomes are presented as risk ratios (RRs). Heterogeneity was explored by χ² and I² (inconsistency) tests. Regression analyses were performed to estimate funnel plot asymmetry. We performed subgroup analyses of patients who were treatment naive, relapers, or nonresponders to previous antiviral treatment. If at least 10 trials were included within each subgroup, we assessed sources of heterogeneity in random-effect meta-regression analyses. These analyses included all the extracted patient, intervention, and trial characteristics. Analyses were performed with the statistical software Review Manager (version 4.2.7; Cochrane Collaboration, Oxford, England), SPSS (version 10.0; SPSS Inc, Chicago, Ill), and Stata (version 8.0; Stata Corp, College Station, Tex).

RESULTS

LITERATURE SEARCH

We identified 774 references through electronic and hand searches (Figure 1). After we read titles and abstracts, we excluded 623 clearly irrelevant references and duplicates and retrieved 155 references for further assessment. Twenty-four references referred to 19 studies that had to be excluded because they were ongoing and data were not yet available or because the reported study design (randomized trial or observational study) was unclear. Seventy-two trials (described in 131 references) fulfilled our inclusion criteria. The trials were published during 1995 to 2004; 19 were published in abstract form and 53 as full articles.

CHARACTERISTICS OF INCLUDED TRIALS AND QUALITY ASSESSMENT

In total, the included trials enrolled 9991 patients. The trials included treatment-naive patients (n=28 trials), relapers (n=9), nonresponders (n=21), treatment-naive patients and relapers (n=1), relapers and nonresponders (n=11), and unknown (n=2). The mean age of the included patients was 42 years (age range, 28-54 years; n=65). The median percentage of patients with cirrhosis was 13% (range, 0%-74%; n=51); of males, 66% (range, 20%-100%; n=62); and of those with hepatitis C virus genotype 1, 66% (range, 0%-100%; n=61). The average patient was diagnosed with chronic hepatitis C according to hepatitis C virus RNA
positivity and elevated transaminase levels or histologic diagnoses. Most trials excluded patients with other liver diseases, alcohol or intravenous drug abuse, and cardiovascular diseases.

Of the included trials, 40% (n = 29) reported adequate allocation sequence generation; 33% (n = 24), adequate allocation concealment; and 21% (n = 15), adequate double-blinding. Only 7% (n = 5) reported adequate allocation sequence generation, allocation concealment, and blinding.

Treatment regimens varied substantially. The dosages of ribavirin were 1000 to 1200 mg daily (n = 52), 800 to 1000 mg daily (n = 11), 600 mg daily (n = 2), 14 to 15 mg/kg per day (n = 6), or unknown (n = 1). The dosages and duration of interferon therapy in the treatment and control groups were similar in 59 trials and differed in 13 trials. The most commonly evaluated intervention regimen was 3 million units of interferon thrice weekly for 4 weeks (n = 28). The types of interferon prescribed were alfa-2b (n = 38), leukocyte (n = 13), alfa-2a (n = 9 trials), pegylated alfa-2b (n = 5), consensus (n = 2), lymphoblastoid (n = 1), or unknown (n = 4).

The median duration of therapy was 29 weeks (range, 6-78 weeks). The median duration of follow-up after treatment was 30 weeks (range, 0-96 weeks).

### EFFECTS OF THE COMPARED INTERVENTIONS

Of 5468 patients receiving combination therapy, 6 died (1 each from colon cancer, drowning, cardiovascular disease, intracranial hemorrhage, and 2 from unknown reasons) and 5 developed cirrhosis. Of 4523 patients receiving monotherapy, 8 died (2 from hepatocellular carcinoma, 1 each from drowning, traffic accident, myocardial infarction, suicide, and 2 from drug overdose, and 12 developed cirrhosis. Compared with monotherapy, combination therapy significantly reduced liver-related morbidity plus all-cause mortality by 54% (Peto OR; 0.46; 95% CI, 0.22-0.96; n = 10 trials) (Figure 2). There was no intertrial heterogeneity (I² = 0%). Combination therapy significantly reduced the risk of liver-related morbidity alone (Peto OR, 0.36; 95% CI, 0.14-0.90) but not of all-cause mortality alone (Peto OR, 0.52; 95% CI, 0.17-1.52).

No statistically significant effects on morbidity plus all-cause mortality were found in subgroup analyses of treatment-naive patients (Peto OR, 0.64; 95% CI, 0.19-2.17), relapsers (Peto OR, 0.13; 95% CI, 0.00-6.78), or nonresponders (Peto OR, 0.42; 95% CI, 0.09-1.92).

Treatment with ribavirin plus interferon significantly reduced the number of patients with failure of sustained virological response compared with treatment with interferon alone (RR, 0.73; 95% CI, 0.71-0.75; n = 30). The intertrial heterogeneity was considerable (I² = 87%). The percentage of patients with failure of sustained virological response after combination therapy was 58% (1575 of 2738 patients) in treatment-naive patients, 51% (328 of 639 patients) in relapsers, and 82% (957 of 1171 patients) in nonresponders. Compared with monotherapy, combination therapy significantly reduced failure of sustained virological response by 29% in treatment-naive patients (RR, 0.71; 95% CI, 0.68-0.74), 40% in relapsers (RR, 0.60; 95% CI, 0.55-0.65), and 15% in nonresponders (RR, 0.85; 95% CI, 0.83-0.88). No significant evidence of publication bias or other biases was found in funnel plot analyses (Eggers test; P = .41). In metaregression analyses, the characteristics of included patients, intervention regimens, methodological quality, and publication status did not seem to be significant predictors of the sustained virological response.

Combination therapy had a significant beneficial effect on histologic response assessed by grading of necro-inflammatory activity (RR, 0.84; 95% CI, 0.80-0.87; n = 9) and fibrosis (RR, 0.95; 95% CI, 0.92-0.97; n = 11). Subgroup analyses of treatment-naive patients, relapsers, and nonresponders were also significant for both outcomes. The percentage of patients receiving combination therapy without improvement in necro-inflammatory activity was 61% in treatment-naive patients (1002 of 1635 patients), 53% in relapsers (86 of 173 patients), and 80% in nonresponders (254 of 318 patients). Per-protocol analyses did not differ significantly from intention-to-treat analyses.

One trial including relapsers found that combination therapy significantly improved quality of life after end of treatment. 30 Two trials including treatment-naive patients allegedly support this finding, but data were not available.

The most common adverse events were hematological (Table 1).
mia occurred in 604 (22%) of 2697 patients receiving combination therapy and in 9 (0.1%) of 2443 receiving monotherapy (RR, 18.22; 95% CI, 12.92-25.70; n = 31). Combination therapy also increased the risk for developing leukopenia and neutropenia. Dermatological, gastrointestinal, and several other miscellaneous adverse events also occurred more frequently during combination therapy. The risk of influenza-like symptoms and depression was not significantly different. Because of adverse events, dosage reductions were necessary for 372 (12%) of 3135 patients receiving combination therapy and for 132 (5%) of 2476 patients receiving monotherapy (RR, 2.25; 95% CI, 1.89-2.68; n = 30). Treatment discontinuations also occurred more frequently among patients randomized to ribavirin plus interferon (645 [15%] of 4425 patients) compared with those randomized to interferon alone (388 [11%] of 3394 patients) (RR, 18.22; 95% CI, 12.92-25.70; n = 31). Combination therapy also increased the risk for developing leukopenia and neutropenia. Large, long-term randomized trials are likely to be planned to assess clinical outcomes. These findings support the robustness of our results but do not exclude the possibility of bias.

The present systematic review suggests that combination therapy to treat chronic hepatitis C infection has both significant beneficial and harmful effects on clinical outcomes. Although the composite outcome of hepatocellular carcinoma, cirrhosis, or death was significantly reduced after combination therapy compared with monotherapy, combination therapy also had significantly beneficial effects on virological markers and histologic response. On the other hand, combination therapy increased the risk of hematological, dermatological, gastrointestinal, and miscellaneous adverse events. Overall, treatment of chronic hepatitis C infection, but patients should first be thoroughly informed about potential adverse events.

The weaknesses of our conclusions are closely linked with the weaknesses in the individual trials. The main concern is the lack of data on long-term follow-up that are necessary to assess clinical outcomes. Large, long-term randomized trials that compare combination therapy with monotherapy or no intervention are necessary to calculate the number of patients needed to treat to prevent 1 patient with end-stage liver disease. Such trials are unlikely to be planned considering the current treatment recommendations. Only 5 (7%) of the 72 included trials reported both adequate randomization and double-blinding, and these aspects may be essential to minimize the risk of bias. However, the impact of bias seems to vary across interventions and diseases. We found no significant association between methodological quality and trial estimates of intervention effects. These findings support the robustness of our results but do not exclude the possibility of bias.

Our previous systematic Cochrane review7 with 48 trials and 6585

### Table 1. Risk of Adverse Events During Treatment With Ribavirin Plus Interferon (Combination Therapy) vs Treatment With Interferon Only (Monotherapy) for Chronic Hepatitis C Infection

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Combination Therapy</th>
<th>Monotherapy</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>194/1070</td>
<td>91/574</td>
<td>1.15 (0.93-1.42)</td>
</tr>
<tr>
<td>Dermatitis*</td>
<td>96/512</td>
<td>29/290</td>
<td>1.64 (1.12-2.40)</td>
</tr>
<tr>
<td>Dry skin*</td>
<td>52/456</td>
<td>27/456</td>
<td>1.93 (1.23-3.01)</td>
</tr>
<tr>
<td>Pruritus*</td>
<td>342/1969</td>
<td>126/1465</td>
<td>1.82 (1.51-2.19)</td>
</tr>
<tr>
<td>Rash*</td>
<td>155/1032</td>
<td>64/1032</td>
<td>2.39 (1.83-3.14)</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>456/1209</td>
<td>342/975</td>
<td>1.05 (0.94-1.17)</td>
</tr>
<tr>
<td>Headache</td>
<td>349/839</td>
<td>231/469</td>
<td>0.95 (0.85-1.06)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>711/1797</td>
<td>555/1290</td>
<td>0.95 (0.95-1.11)</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>589/1325</td>
<td>516/1052</td>
<td>1.08 (1.00-1.16)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>108/1276</td>
<td>121/1005</td>
<td>0.81 (0.63-1.04)</td>
</tr>
<tr>
<td>Anorexia/nausea*</td>
<td>517/1970</td>
<td>364/1467</td>
<td>1.20 (1.08-1.34)</td>
</tr>
<tr>
<td>Diarrhea/constipation</td>
<td>183/1554</td>
<td>200/1280</td>
<td>0.84 (0.70-1.00)</td>
</tr>
<tr>
<td>Dyspepsia*</td>
<td>81/721</td>
<td>45/717</td>
<td>1.78 (1.26-2.51)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>107/1213</td>
<td>99/940</td>
<td>1.00 (0.76-1.31)</td>
</tr>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia*</td>
<td>604/2697</td>
<td>19/2443</td>
<td>18.22 (12.92-25.70)</td>
</tr>
<tr>
<td>Leukopenia*</td>
<td>16/47</td>
<td>3/45</td>
<td>4.32 (1.56-11.90)</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>59/1143</td>
<td>17/617</td>
<td>1.67 (1.00-2.77)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8/6057</td>
<td>7/368</td>
<td>0.86 (0.33-2.22)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex*</td>
<td>3/96</td>
<td>2/92</td>
<td>1.37 (1.29-6.52)</td>
</tr>
<tr>
<td>Pharyngitis*</td>
<td>91/649</td>
<td>60/648</td>
<td>1.51 (1.11-2.06)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>43/456</td>
<td>48/456</td>
<td>0.90 (0.61-1.32)</td>
</tr>
<tr>
<td>Psychological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>438/3343</td>
<td>330/2456</td>
<td>1.07 (0.94-1.21)</td>
</tr>
<tr>
<td>Insomnia*</td>
<td>487/1875</td>
<td>276/1366</td>
<td>1.39 (1.22-1.58)</td>
</tr>
<tr>
<td>Irritability</td>
<td>323/1691</td>
<td>214/1183</td>
<td>1.10 (0.94-1.29)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>309/1103</td>
<td>257/871</td>
<td>0.96 (0.96-1.10)</td>
</tr>
<tr>
<td>Cough*</td>
<td>145/1503</td>
<td>71/1236</td>
<td>1.82 (1.38-2.39)</td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>147/1262</td>
<td>63/923</td>
<td>1.98 (1.49-2.62)</td>
</tr>
<tr>
<td>Fatigue/weakness*</td>
<td>1002/1963</td>
<td>675/1464</td>
<td>1.12 (1.05-1.20)</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>17/773</td>
<td>10/500</td>
<td>0.85 (0.43-1.65)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>5/101</td>
<td>5/103</td>
<td>0.99 (0.33-1.65)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*The risk ratio significantly contraindicated combination therapy (P<.05).
patients found no significant effect on morbidity or mortality from adding ribavirin to interferon. However, updating this review with 24 new trials that included 3406 patients led to significant results on this outcome. The robustness of this primary outcome is supported by analyses that include only liver-related morbidity or mortality and analyses that include trials with the same interferon schedule in both treatment arms. Furthermore, we had a posttreatment mean follow-up of only 30 months. To evaluate the full impact of combination therapy, one needs a longer follow-up period. On the other hand, our findings may have some weaknesses. First, cirrhosis might not be considered a clinical outcome if assessed by, for example, liver biopsy. However, we were unable to establish the method by which cirrhosis was diagnosed. Second, the result is based on a composite outcome with a different relevance for patients. Combination therapy showed no significant effect on all-cause mortality alone. Third, Peto OR analyses do not include the majority of trials, which obtained no events on mortality or morbidity. However, risk difference analyses, which include trials with no events, also found a significant risk reduction (−0.20%; 95% CI, −0.31% to −0.01%).

Fourth, we kept in mind that the effect of interferon monotherapy on morbidity or mortality is not clearly established. Accordingly, we lacked this important information when assessing the benefits and harms of combination therapy.

We have assessed multiple outcomes in the updated review, which increases the risk of type I errors. All of our significant findings had very low P values except for morbidity plus mortality (P = 0.03). This decreases the risk of spurious P values for most outcomes, but we cannot exclude the possibility that our findings on morbidity plus mortality may represent a type I error. In the future, one way to reduce the risk of type I errors in cumulated meta-analyses may be to conduct trial sequential analysis.

Combination therapy has significant beneficial effects on virological markers and histologic response. Observational studies have reported that morbidity is reduced among virological responders. Furthermore, our short-term histologic results seem encouraging and suggest that combination therapy may delay development of cirrhosis. The average patient with chronic hepatitis C infection develops cirrhosis in approximately 30 years. However, older age, viral coinfections, alcohol abuse, male sex, and being overweight are some factors that may worsen long-term outcomes.

Even in the absence of complications, a chronic hepatitis C infection may impair a patient’s quality of life. Three included trials found that combination therapy significantly increased virological response and improved quality of life. Accordingly, the effects of treatment on quality of life are likely to be related to virological response rates. However, we were unable to obtain data on quality of life from 2 included trials and 1 study found that quality of life was impaired in patients with seropositive hepatitis C virus only if they were aware of their serostatus. Future studies on antiviral treatment for patients with chronic hepatitis C infection should address quality-of-life issues.

Ribavirin and interferon are both associated with various adverse events. This review highlights several adverse events induced by ribavirin. Accordingly, dosage reduction of ribavirin should be the first choice if these specific adverse events occur. By lowering the dosage of ribavirin, the virological response rate is not necessarily affected in patients with, for instance, genotypes 2 and 3 or low viral load. Furthermore, the most common hematological adverse events related to combination therapy may also be reduced with epoetin alfa. However, our review may in general underestimate the risk of adverse events. First, the reporting of adverse events in many randomized clinical trials is of poor quality. Second, the follow-up time was only 30 weeks, and subsequent adverse events related to combination therapy might not have been identified. Finally, 19 (26%) of 72 trials were published as abstracts, which limits the available information on adverse events.

The included patients and intervention regimens varied substan-

Table 2. Effects of Ribavirin Plus Interferon vs Interferon for Chronic Hepatitis C Infection, Number Needed to Treat (NNT) and Number Needed to Harm (NNH)*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NNT (95% CI)†</th>
<th>NNH (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality/morbidity</td>
<td>444 (302-5650)</td>
<td>1</td>
</tr>
<tr>
<td>Clearing of HCV-RNA</td>
<td>4 (4-6)</td>
<td>111</td>
</tr>
<tr>
<td>Improving histologic response</td>
<td>8 (7-100)</td>
<td>56</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (4-5)</td>
<td>111</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4 (3-7)</td>
<td>111</td>
</tr>
<tr>
<td>Rash</td>
<td>11 (9-17)</td>
<td>40</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13 (10-20)</td>
<td>34</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14 (8-20)</td>
<td>32</td>
</tr>
<tr>
<td>Dose reductions</td>
<td>14 (11-17)</td>
<td>32</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>14 (8-50)</td>
<td>32</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17 (11-25)</td>
<td>26</td>
</tr>
<tr>
<td>Fatigue/weakness</td>
<td>17 (11-33)</td>
<td>26</td>
</tr>
<tr>
<td>Dry skin</td>
<td>20 (11-50)</td>
<td>22</td>
</tr>
<tr>
<td>Anorexia/nausea</td>
<td>20 (13-50)</td>
<td>22</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>20 (13-50)</td>
<td>22</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>20 (13-100)</td>
<td>22</td>
</tr>
<tr>
<td>Cough</td>
<td>20 (14-33)</td>
<td>22</td>
</tr>
<tr>
<td>Stop treatment</td>
<td>50 (33-100)</td>
<td>9</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HCV, hepatitis C virus.
*Number needed to treat to obtain 1 more beneficial outcome.
†Number needed to treat to obtain 1 more harmful outcome.
‡Number of patients who obtain the outcomes when treating 444 patients.
§Number of patients who obtain the outcomes when treating 444 patients.
tially. We performed metaregression analyses to explore the intertrial heterogeneity, which was considerable in several meta-analyses, but we were unable to identify variables significantly associated with virological response. We aimed to assess the effect of adding ribavirin irrespective of type and dosage of interferon. The most common regimen was 3 million units of interferon-alfa thrice weekly. Recent trials found significantly higher sustained response rates after treatment with pegylated interferon that was administered once weekly, without apparently increasing the risk of adverse events.32,55

The beneficial effect of adding ribavirin to interferon treatment is not fully understood. Ribavirin monotherapy does not seem to have an effect on viral clearance of hepatitis C but is associated with adverse events.30 On the other hand, adding ribavirin to interferon therapy clearly increases the number of patients with virological response as well as the number of adverse events. Both benefits and adverse events of adding ribavirin to interferon treatment for patients with chronic hepatitis C should be considered before therapy is started.

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Additional Information: Dr Brok, as the principal investigator of this study, had complete access to the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. This work for this article was carried out using the recommendations of the Cochrane Collaboration and the Cochrane Hepato-Biliary Group. This review will be published in the Cochrane Database of Systematic Reviews. Cochrane Reviews are regularly updated as new evidence emerges and in response to comments and criticisms.

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REFERENCES