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Interferon-based Therapies for Chronic Hepatitis C Virus Infection: An Assessment of Clinical Outcomes

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Inteferon-based Therapies for Chronic Hepatitis C Virus Infection: An Assessment of Clinical Outcomes

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May 2004

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Authorship

Donald Husereau and Ken Bassett developed the research protocol. Ronald Koretz reviewed the protocol, made suggestions and approved its final draft. Donald Husereau and Ken Bassett individually abstracted data from trial reports. Ronald Koretz, Ken Bassett and Donald Husereau each contributed to the report up to its final draft.

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Conflicts of Interest

For all authors: no competing interests.

REPORT *IN BRIEF*

April 2004

Interferon-based Therapies for Chronic Hepatitis C Virus Infection: An Assessment of Clinical Outcomes

Technology Name

Interferon (IFN)-based antiviral therapies:

- standard IFN plus ribavirin versus standard IFN therapy alone
- standard IFN plus ribavirin versus pegylated IFN plus ribavirin

Disease/Condition

Chronic hepatitis C virus (HCV) infection

Technology Description

IFNs are human proteins that inhibit virus replication in infected cells and boost the natural antiviral capacity of the infected patient. Pegylated IFNs are chemically altered so that they stay inside the body longer. Ribavirin is a synthetic nucleoside analogue thought to inhibit viral reproduction.

The Issue

New Canadian guidelines recommend pegylated IFN alfa plus oral ribavirin as standard treatment for chronic HCV infection. While morbidity and mortality data are needed for properly informing patients and conducting effectiveness and cost-effectiveness analysis, previous reviews of these therapies do not provide this information.

Assessment Objectives

We explored the effectiveness of IFN-based treatments by examining mortality and serious morbidity during chronic HCV infection treatment. We also considered the withdrawals due to adverse events, quality of life and the virologic markers related to use of the following recommended treatments:

- standard IFN plus ribavirin versus standard IFN therapy alone
- standard IFN plus ribavirin versus pegylated IFN plus ribavirin.

Methods

This review is based on an Agency for Healthcare Research and Quality (AHRQ) systematic review. Studies were re-examined for morbidity and mortality data. In addition, supplemental trial reports were identified from bibliographic databases, manufacturers' information and from the US Food and Drug Administration's web site. Data were sought on life-threatening events observed during trials and withdrawals due to adverse events. Surrogate outcomes, including viral response and quality of life measures, were also sought. Individual trial quality was not assessed.

Conclusions

- Information on quantity or quality of life related to IFN-based treatment is lacking.
- Morbidity and mortality after therapy with ribavirin added to standard IFN could not be estimated from the randomized trial evidence.
- Pegylated IFN combined with ribavirin can increase the need for urgent medical attention when compared with standard IFN plus ribavirin.
- Pegylated IFN plus ribavirin therapy can reduce the risk of persistent viremia and liver enzyme elevation to the greatest degree, when it is compared with standard IFN plus ribavirin therapy or with standard IFN therapy alone.

This summary is based on a comprehensive health technology assessment available from CCOHTA's web site (www.ccohta.ca): Husereau D, Bassett K, Koretz R. *Interferon-based therapies for chronic hepatitis C virus infection: an assessment of clinical outcomes.*

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EXECUTIVE SUMMARY

The Issue

An estimated 204,000 to 282,000 Canadians have chronic hepatitis C virus (HCV) infection. Of this group, 9% to 30% will develop complications such as cancer and cirrhosis. While there is no evidence that altering surrogate endpoints (such as viral load; and biochemical or histological markers) with interferon (IFN)-based treatment prevents complications, 2004 Canadian guidelines recommend pegylated IFN alfa plus oral ribavirin as standard treatment for chronic HCV infection. Systematic reviews have evaluated the impact of treatment on these surrogate endpoints and have omitted an adequate analysis of outcomes such as mortality and serious morbidity. These data are essential for properly informing patients and for conducting effectiveness and cost-effectiveness analyses.

Objective

This review explores the effectiveness of IFN-based combination drugs by examining mortality and serious morbidity during the treatment of chronic HCV infection. We also consider the withdrawals due to adverse events, the quality of life and the virologic markers related to use of the following recommended treatments:

- standard IFN plus ribavirin versus standard IFN therapy alone
- standard IFN plus ribavirin versus pegylated IFN plus ribavirin.

Methods

This review is based on an Agency for Healthcare Research and Quality (AHRQ) systematic review. Studies were re-examined for morbidity and mortality data. In addition, supplemental trial reports were identified from bibliographic databases, manufacturers' information and from the US Food and Drug Administration's (FDA) web site. Data were sought on primary outcomes related to life-threatening events that resulted in disability, hospitalization or death; and withdrawals due to adverse events (AEs). Surrogate outcomes, including withdrawals due to AEs, quality of life and virologic markers, were also sought. These data were abstracted independently by two reviewers and combined by meta-analysis using Metaview 4.1. A Peto odds ratio (OR) was calculated for rare outcomes, such as death; and a relative risk, absolute risk or rate ratio was calculated for other outcomes. A chi-square test for statistical heterogeneity was performed for each outcome. Individual trial quality was not assessed.

Results

Standard IFN plus ribavirin versus standard IFN therapy alone: Fifty reports describing 51 trials (n=7,474) that randomized at least one treatment arm to receive standard IFN plus ribavirin and another to receive standard IFN alone were identified in the AHRQ review. Sixteen trials were reported in conference abstract form only.

Inconsistencies in viral response rates between RCTs were sufficiently large that the reliability of a meta-analysis for this outcome was questionable. These inconsistencies disappeared, however, when only trials with IFN-naïve patients (the same patients enrolled in all pegylated IFN trials) were considered. Among these individuals, one extra case of chronic HCV infection was

prevented for every five (95% CI: 4.1 to 5.0) patients treated with combination therapy. The relative risk (RR) of not achieving a virologic response was reduced by 27%.
Mortality and serious adverse event (SAE) rates could be determined from 16% (8/51) of RCTs; all these were less than 72 weeks in length. When pooled, no statistically significant difference was detected in occurrences of all-cause mortality (Peto OR, 0.37, 95% CI: 0.08 to 1.67) or SAEs (RR 1.02, 95% CI: 0.84 to 1.24). No trial reported the impact of treatment on patients' quality of life.

Data on withdrawals due to AEs were available from 59% (30/51) of RCTs. The addition of ribavirin to standard IFN caused a 2% absolute increase in the proportion of withdrawals due to AEs. This implies that an extra patient is required to withdraw after initiating therapy, because of AEs, for every 50 patients treated with combination therapy compared to IFN alone.

Standard IFN plus ribavirin versus pegylated IFN plus ribavirin: Two multi-centre RCTs 72 weeks in length that randomized 2,729 IFN-naïve patients diagnosed with chronic hepatitis were identified and the results for each outcome combined.

No statistically significant differences in proportions of patients dying were detected (Peto OR, 0.30, 95% CI: 0.03 to 3.14). A significantly higher rate of serious morbidity (non-fatal SAEs) occurred in the pegylated IFN plus ribavirin combination therapy group compared with the IFN alfa-2b plus ribavirin control group (rate ratio=1.24, 95% CI: 1.01 to 1.51).

An increase or decrease in withdrawals due to AEs (including death and laboratory abnormalities) could not be detected (fixed effects estimate of RR 0.97, 95% CI: 0.75 to 1.24). Patients' quality of life was measured in one trial, but the results were not interpretable.

The RR of not achieving a measurable response was reduced by 13% (RR 0.87, 95% CI: 0.80 to 0.94) in these two trials. In absolute terms, one additional patient avoided chronic HCV infection for every 14 patients treated with pegylated IFN combined with ribavirin instead of standard IFN combined with ribavirin.

Conclusions

- Information on quantity or quality of life related to IFN-based treatment is lacking.
- Morbidity and mortality after therapy with ribavirin added to standard IFN could not be estimated from the randomized trial evidence.
- Pegylated IFN combined with ribavirin can increase the need for urgent medical attention when compared with standard IFN plus ribavirin.
- Pegylated IFN plus ribavirin therapy can reduce the risk of persistent viremia and liver enzyme elevation to the greatest degree, when it is compared with standard IFN plus ribavirin therapy or with standard IFN therapy alone.

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1 INTRODUCTION

1.1 Background

An estimated 204,000 to 282,000 or 0.8% of Canadians are infected with the hepatitis C virus (HCV).[1] There is a lack of reliable national incidence data, but it has been estimated that between 3,000 and 6,000 Canadians are newly diagnosed every year.[2] Most cases (80%) are thought to be the result of injection drug use.[2] It is estimated that 15% of infected adults will immediately clear the virus; the remainder will have persistent viremia (chronic HCV infection).[3-7] Many chronically infected individuals are asymptomatic and some spontaneously clear the virus.[8] An estimated 9% to 30% of patients with chronic HCV infection will develop serious complications such as liver disease (cirrhosis and hepatocellular carcinoma) over several decades.[5-16]

Few treatment options exist for individuals with chronic HCV infection. Some newer drugs[17] and medicinal herbs[18] are still investigational. Established treatments range from lifestyle counselling (losing weight, avoiding alcohol) to the use of antiviral prescription drugs.[19] Antiviral prescription drug therapy was limited to the use of interferon (IFN). Recently introduced strategies include combining oral ribavirin with IFN ("combination therapy") and conjugating IFN with polyethylene glycol ("pegylated IFN").

Since it takes decades for serious complications to occur and since a minority of infected patients develop them, any randomized trial comparing treatment to no treatment would require large numbers of patients and take decades to complete. Most hepatologists believe that the undertaking of such a project would be impractical. Instead, surrogate or intermediate measurements of biochemical (e.g., alanine transaminase), histologic (e.g., fibrosis) or virologic (HCV-RNA) markers have been used as study endpoints. Information is lacking from prospective controlled trials to show that alterations in these outcomes affect the incidence of liver cancer, liver failure or death. Rather, the use of surrogates has been supported by inferences from observational studies or pathophysiological theory.[20-24]

The effect of antiviral therapy on chronic HCV infection has been assessed in systematic reviews and meta-analyses of evidence from randomized controlled trials (RCTs). Most reviews provide an estimate of potential benefit in terms of intermediate or surrogate outcomes, but an adequate analysis of mortality and serious morbidity effects is lacking in most reports (Table 1). This reflects empirical evidence that suggests systematic reviews lack proper reporting of serious adverse events (SAEs).[25] Ignoring mortality and serious morbidity could introduce unnecessary bias when assessing risk versus benefit. Mortality and serious morbidity information is also essential for conducting robust cost-effectiveness analyses.

Table 1: Systematic reviews and meta-analyses of ribavirin combined with pegylated or standard IFN

Systematic Review Author, Year	Database Searched or Search Strategy, Timeline	Number of Trials/ Number of Patients (Design and publication characteristics)	Serious Morbidity and Mortality	Adverse Events and Quality of Life	Surrogate Outcomes
IFN and ribavirin versus IFN					
Schalm, 1999[26]	Meta-analysis of individual patient data	6/344 (RCT)		WDAEs, DRAE, hemolysis	SVR (normal ALT and no HCV RNA) after 6 months
Poynard, 2000[27]	Meta-analysis of individual patient data from 3 RCTs	3/1,744 (RCT)			ALT and no HCV-RNA, portal fibrosis
Shepherd, 2000[28]	MEDLINE®, pre-MEDLINE, EMBASE, DARE, 1996 to end of 1999; Cochrane Controlled Trials Register, 1993 to 2000; industry submissions	19/3,418 (RCT, published or unpublished)		WDSAE, AEs from some trials	SVR
Cheng, 2001[29]	MEDLINE®, January 1996 to June 2000	7/766 (RCT, published)			ETBR, ETVR, SBR, SVR, histologic response
Cummings, 2001[30]	MEDLINE®, January 1966 to December 1999; SciSearch®; manual search of reference lists and journals; experts	12/1,070 (RCT, published)	Treatment-related deaths	WDAEs, DRAEs, AEs	Virologic response, biochemical response, histologic response
Kjaergard, 2001, updated in 2003[31]	MEDLINE®, 1966 to August 2001; EMBASE, 1985 to August 2001; Cochrane Hepato-Biliary Group Controlled Trials Register; hand searches; contact with industry	48/6,585 (RCT, published or unpublished)	Mortality and liver-related morbidity	AEs, WDAEs, treatment discontinuations, quality of life	SVR, ETVR, ETBR, SBR, histologic response
Gebo, 2002[32]	PubMed, BIOSIS Previews®, SciSearch, MANTIS™, Allied and	54/7,173 (RCT, full papers, systematic reviews)		WDAEs, DRAEs	ETBR, SBR, ETVR, SVR, histologic response

Systematic Review Author, Year	Database Searched or Search Strategy, Timeline	Number of Trials/ Number of Patients (Design and publication characteristics)	Serious Morbidity and Mortality	Adverse Events and Quality of Life	Surrogate Outcomes
	Complementary Medicine™ Database, CAB Health, PsycINFO®, Sociological Abstracts				
Pegylated IFN plus ribavirin versus IFN plus ribavirin					
Gebo, 2002 (published as Chander, 2002)[33]	PubMed, BIOSIS Previews®, SciSearch, MANTIS, Allied and Complementary Medicine™ Database, CAB Health, PsycINFO, Sociological Abstracts	2/2,651 (RCT, full papers)		WDAEs, DRAEs	ETBR, SBR, ETVR, SVR, histologic response

ETBR=biochemical (marker) response at end of treatment; AE=adverse event; SBR=biochemical marker response at given time (e.g., six months) after cessation of treatment; ETVR=viral RNA detectable at end of treatment; SVR=viral RNA detectable at given time (e.g., six months) after cessation of treatment; WDAE=withdrawals due to adverse events; DRAE=dosage reductions (adjustments) due to adverse events; ALT=alanine transaminase enzyme; RCT= randomized controlled trials; WDSAE=withdrawals due to serious adverse events.

This review focuses on the effectiveness of IFN-based combination drug treatment of chronic HCV infection. We clarify the strengths and limitations of published and unpublished evidence and provide a balanced look at systematic reviews of drug efficacy. Mortality and serious morbidity data are essential for properly informing patients and conducting effectiveness and cost-effectiveness analyses.

2 OBJECTIVE

This review explores the effectiveness of IFN-based combination drugs by examining mortality and serious morbidity during the treatment of chronic HCV infection. We also consider the withdrawals due to adverse events, the quality of life and the virologic markers related to the use of the following recommended treatments:

- standard IFN plus ribavirin versus standard IFN therapy alone
- standard IFN plus ribavirin versus pegylated IFN plus ribavirin.

We focus on outcomes that resulted from the use of recommended dosages in treatment-naïve patients, but we also explore the effects from alternative dosages and in different patient populations. We highlight the reported number of patients who achieved researcher-defined threshold improvements in quality of life and virologic measurements.

2.1 Technology Overview

IFN alfa may be obtained from leukocytes or lymphoblasts and through recombinant deoxyribonucleic acid (DNA) technology. IFN alfa-2a (Roferon™-A) and IFN alfa-2b (Intron A™) are proteins composed of 165 amino acids. They differ by one amino acid residue. IFN alfacon-1 (Infergen®) is a recombinant type 1 IFN that differs from naturally occuring IFN alfa-2 at 20/166 amino acids and that has similarities to IFN beta. Their biological effects are similar. The pegylated forms of IFN alfa-2a (Pegasys™) and IFN alfa-2b (PEG-Intron™) differ in the molecular weight and structure of the polyethylene glycol conjugate. Pegylated IFNs, which stay in the body longer, have been proposed because of the potential for an increased duration of therapeutic activity.

IFNs bind to specific membrane receptors on the surface of cells and initiate a complex sequence of intracellular events that include the induction of certain enzyme systems. This process is at least partly responsible for slowing virus replication in infected cells and increasing the natural antiviral activity (e.g., phagocytic activity of macrophages) in the human host.[34]

Ribavirin is a synthetic nucleoside analogue that has shown in vitro activity against some, but not all, ribonucleic acid (RNA) and DNA viruses. Its mode of action is unclear, but it may interact with cellular enzymes and inhibit viral nucleic acid synthesis.[34] At physiologic concentrations, neither ribavirin nor its intracellular nucleotide metabolites inhibit HCV replication. Ribavirin monotherapy has no effect on the levels of serum HCV or on hepatic histology after six to 12 months of therapy and five months of follow-up.[35] Ribavirin combined with IFN, however, has shown increased efficacy compared with IFN alone, as measured by a reduced viral load.[31]

2.1.1 The issue

Several therapies are approved for chronic HCV infection in Canada (Table 2). According to 2004 Canadian consensus guidelines, the recommended treatment is the combination of pegylated IFN alfa (-2a or -2b) plus oral ribavirin.[36] The recommended dose of ribavirin is 1,000

mg for patients weighing less than 75 kg and 1,200 mg daily for patients weighing more than 75 kg. Treatment duration with IFN and ribavirin is determined by the viral genotype. Patients who carry genotypes 2 or 3 may be treated for 24 weeks with a ribavirin dose of 800 mg daily. Patients carrying genotype 1 should be treated for 48 weeks only if a 2 log drop or undetectable HCV RNA is achieved after 12 weeks.[36] Those with a 1.8 to 2.0 log drop should be reassessed at 24 weeks and their treatment discontinued if a response is not achieved by that time.[36]

Current guidelines suggest that treatment should be considered for all patients who test positive for HCV-RNA, regardless of the apparent state of their liver disease. The decision maker should reconsider factors such as the risk for liver disease progression, likelihood of treatment response, risk of adverse effects, symptoms and the patient's wishes. Patients with decompensated liver failure, who are abusing alcohol, who are pregnant or who lack appropriate contraception should not receive therapy.[36]

Table 2: Health Canada-approved IFN-based products for chronic HCV infection

Class	Drug	Dosage	Duration	Cost for One Course of Therapy
IFN Monotherapy	IFN alfa-2a (Roferon®-A)	6 MIU 3 times/week for 3 months then 3 MIU 3 times/week	24 weeks	C$3,672
	IFN alfa-2b (Intron A)	3 MIU 3 times/week	48 to 84 weeks	C$4,894 to C$7,341
	IFN alfacon-1 (Infergen®)	9 mcg 3 times/week	24 weeks	C$2,326 to C$3,880
Pegylated IFN	Pegylated IFN alfa-2b (Unitron-Peg™)	1 mcg/kg/week	48 weeks	C$19,000
	Pegylated IFN alfa-2a (Pegasys)	180 mcg once weekly	48 weeks	C$19,000
Combination Therapy	IFN alfa-2b plus ribavirin (Rebetron®)	INF: 3 MIU 3 times/week Rib: 1,000 to 1,200 mg/day (based on weight)	24 to 48 weeks: discontinue if no virologic response after 24 weeks	C$9,026 to C$19,948
	Pegylated IFN alfa-2b plus ribavirin (Pegetron™)	Peg: 1.5 mcg/kg/week Rib: 800 to 1,200 mg/day (based on weight)	24 to 48 weeks: discontinue if no virologic response after 6 months	C$9,026 to C$19,948
	Pegylated IFN alfa-2a plus ribavirin	*A combination product is not marketed in Canada.*		

MIU=millions of International units; mcg=microgram; Peg=pegylated IFN; Rib=ribavirin

3 CLINICAL REVIEW

3.1 Methods

3.1.1 Literature search

Systematic reviews and reports of drug therapy for chronic hepatitis C were identified by searching PubMed, the Cochrane Library, the web sites of health technology assessment and other agencies (such as the Agency for Healthcare Research and Quality (AHRQ), specialized databases (such as the NHS Centre for Reviews and Dissemination) and trial registries (such as Current Controlled Trials) and by manually searching the bibliographies of retrieved reports. In addition, a Dialog® OneSearch® on MEDLINE®, TOXLINE®, EMBASE and BIOSIS Previews® was performed to obtain reports of safety (see Appendices 1 and 2 for full search strategy).

3.1.2 Selection criteria and method

We did not conduct an independent systematic review of the research literature. Instead, reports of RCTs were identified from the bibliography of a systematic review conducted in 2002 by the AHRQ.[32] All reports included in the AHRQ report had been identified in previous systematic reviews. In additon, the questions that the review sought to answer were similar to ours. As a result, the review was judged to be the most relevant and comprehensive. The manufacturer of ribavirin with IFN alfa-2b and ribavirin with pegylated IFN alfa-2b (Schering Canada) was asked to provide additional information about safety and new trials. We did not contact the manufacturer of pegylated alfa-2a, as a licensed product was unavailable in Canada at the time of our review.

3.2 Data Extraction Strategy

Characteristics of trials, participants, interventions and outcomes were abstracted by two reviewers (DH and KB) independently using a standard form (Appendix 3). Outcomes were also abstracted independently by each reviewer using an electronic spreadsheet. Disagreements were resolved by re-examining the original trial reports and using forced consensus. Abstracted data were also compared to previously abstracted data from systematic reviews (e.g. withdrawals due to adverse events) to check for consistency. Missing data were supplemented from tertiary reports, including Food and Drug Administration (FDA) documents. We planned to use a third party to resolve persisting differences, but no such differences developed. The authors and titles of the reports were not masked from the reviewers during data abstraction.

3.3 Data Analysis Methods

Statistical analysis was performed on an intention-to-treat basis using methods similar to those used in a previous Cochrane meta-analysis. The intention-to-treat population was defined as the population initially randomized to each treatment arm. Cochrane Review Manager 4.1 software with MetaView 4.1 was used to calculate combined outcomes. Outcome data for rare events such

as mortality were combined using a Peto odds ratio method. Random effects (DerSimonian and Laird) and fixed effects (Mantel-Haenszel) models were used for combining other dichotomous outcomes. These were expressed as relative risks (RR), absolute risk differences (ARD) and 95% confidence intervals. When dichotomous outcome data were unavailable but an incidence was reported, a rate ratio was calculated and combined using a fixed effects model.

Statistical heterogeneity across trials was assessed using a chi-square test. When statistical heterogeneity was present ($p<0.1$), a random effects model was applied and the results of combining the outcome data using fixed and random effects models were shown for comparison. We sought to explain heterogeneity for primary outcomes by identifying potential sources a priori. These included dosage, duration of treatment and characteristics of patients (including genotype and previous response to or relapse after treatment). The detection of statistical heterogeneity, however, was limited when a low number of RCTs were included.

3.4 Clinical Outcomes

The health outcome data extracted from the RCTs are organized in order according to clinical significance.

Primary Outcomes
Mortality and serious morbidity from all causes were estimated using the occurrence of serious adverse events (SAEs) during treatment. These were most often defined as fatal or life-threatening experiences that were observed during the trial and that resulted in disability or hospitalization. These included disease-specific events (new incidence of hepatic cirrhosis, hepatocellular carcinoma, liver failure, liver transplantation) and general health effects (hospitalizations, infections, psychiatric events). We accepted any investigator's definition of a SAE.

Secondary Outcomes
- withdrawals due to adverse events
- quality of life
- virologic markers.

4 RESULTS

4.1 Quantity and Quality of Research Available

The most current and comprehensive systematic review identified was prepared for the AHRQ by Gebo *et al*.[32] A literature search strategy covering eight electronic biomedical and social sciences databases was described in the report. Search terms were limited to controlled vocabulary (i.e. controlled subject headings). Consequently, the sensitivity of the search would be limited if text-words were excluded. Eligibility criteria for trial selection were described in the report and measures to prevent bias in the selection of studies were outlined. Trial reports were limited to those in English and abstracts were excluded. Systematic reviews were not quality scored. The criteria used to assess the validity of the individual studies were reported. No attempt was made to perform a meta-analysis or to quantitatively combine data for any of the study questions; the reasons for this were unstated. Thus, no strategy to detect publication bias was outlined. Unique trials identified from the AHRQ review are shown in Appendix 4.

Standard IFN plus ribavirin versus IFN therapy alone: From the AHRQ systematic review, 50 reports describing 51 trials (n=7,474) that randomized at least one treatment arm to receive standard IFN plus ribavirin and another to receive standard IFN alone were identified. These trials could be categorized by the type of patient enrolled (Table 3). One report[37] described the combined outcomes of two trials[38] and an additional trial[39] used a stratified randomization scheme to analyze non-responders separately from relapsers. Sixteen trials[40-55] were reported in conference abstract form only.

Standard IFN plus ribavirin versus pegylated IFN plus ribavirin: The AHRQ systematic review identified two unique trials that randomized 2,729 patients with chronic hepatitis C to either ribavirin plus pegylated IFN, placebo plus pegylated IFN or ribavirin plus standard IFN (Table 3). In addition, these patients did not have advanced liver disease or co-existing morbidities such as human immunodeficiency virus or hepatitis B virus. Of these patients, 2,502 were randomized to receive either ribavirin plus pegylated IFN or ribavirin plus standard IFN and 2,427 received at least one dose. Both trial reports were published in medical journals and supplementary information was retrieved from the FDA's web site.[56-58] Both trials included patients who were newly diagnosed and had no prior exposure to IFN therapy (naïve) (Appendix 4).

Table 3: Patients' characteristics from identified RCTs

Patients' Characteristics, Dosage	Number of Trials (comparisons)*	Number of Participants	Average Age Across Trials	Number of Males (% of males)	Viral Genotype 1a/1b (%)
IFN plus ribavirin IFN alone					
Naïve (no previous IFN therapy)	12[41,45,54,59-67]	3,145	42.7[a] (34 to 50)	1,810[a] (64.3)	1,870[b] (63.3)
Non-responders (no biochemical or virological response) to previous therapy	23*[39,40,42,44,50,52,53,55,68-82]	2,579	44.3[c] (33.7 to 53)	1,380[c] (69.3)	1,237[d,e] (65.2)
Relapsers (response to previous IFN therapy with subsequent elevation of biochemical or virological markers)	6*[37,39,43,46,83]	713	37.5[f]	472[f] (81.8)	342[g] (50.5)
Non-responders and relapsers with treatment modified according to initial response to therapy	4[47,49,84,85]	704	41.8¥	372¥ (71.6)	307¥ (59.0)
Non-responders and relapsers randomized together	3[86-88]	152	43.75[h]	90 (64.2)	unable to estimate
Naïve and relapsers randomized together	1[89]	25	38.7	NR	NR
Unknown characteristics	3[48,51,90]	162	42‡	unable to estimate	unable to estimate
Standard IFN plus ribavirin versus pegylated IFN plus ribavirin					
Naïve (no previous IFN therapy)	2[56-58,91]	2,729	42.6 to 44	1,803 (66)	1,768 (64.8)

*Barbaro 1999 is counted twice due to the stratified randomization scheme, which allows for two patient group comparisons, so the number of trials is 51, whereas the total number of trial arm comparisons is 52 a) reported in 9 trials[54,59-62,64-67] (2,812 patients) only; b) reported in all but one trial report[84] c) information unavailable from four trial reports[42,52,55,77]; d) unreported in five trials[42,50,52,53,78] e) one trial[77] genotyped 100 out of 126 individuals; f) two reports[43,46] do not provide this information; g) one report[43] does not provide this information; ¥ information available from three trials[47,49,85] only; ‡information available from two reports[51,90] only; h) unavailable from one report.[86]

4.2 Data Analysis and Synthesis

4.2.1 Mortality and serious morbidity

Table 4: Analysis of primary clinical outcomes

	Number of Trials Reporting Outcome† (% of all trials)	Number of Participants Randomized (% of all trial participants)	Statistical Method, Effect Size (95% CI)	Absolute Risk Difference, % (95% CI)
Standard IFN plus ribavirin versus standard IFN alone		7,474 (100)		
All-cause mortality	8*(15.7)	2,400 (32.1)	Peto OR, 0.37 (0.08 to 1.67)	0 (-1 to 0)
All-cause serious morbidity	8* (15.7)	2,204 (29.5)	RR, 1.02 (0.84 to 1.24)	0 (-3 to 3)
Pegylated IFN plus ribavirin versus standard IFN plus ribavirin		2,502‡ (100)		
All-cause mortality†	2 (100)	2,502‡ (100)	Peto OR, 0.30 (0.03 to 3.14)	0 (0 to 0)
All-cause serious morbidity	2 (100)	2,502‡ (100)	RateR, 1.24 (1.01 to 1.51)	N/A

‡These patients were randomized and received at least one dose; †If a trial report stated that all patients completed treatment, we assumed zero deaths had occurred; *Results of two trials were combined in one report;[37] NNT_H =number needed to treat to harm; OR=odds ratio; RateR=rate ratio; RR=relative risk. Of 2,729 participants enrolled in trials, 2,502 patients were randomized to receive either ribavirin plus pegylated IFN or ribavirin plus standard IFN; N/A=not applicable.

4.2.2 All-cause mortality (fatal SAEs)

Standard IFN plus ribavirin versus IFN therapy alone (Table 4 and Appendix 5, Figure 1a): All-cause mortality data were available from 16% (8/51) trials. Two reports (three trials)[37,62] explicitly reported this outcome and three others[60,72,84] implied no deaths had occurred by either stating that no SAEs occurred or that all patients completed follow-up. Information about death from two other trials[64,66] was obtained from supplementary information[38] (Table 5).

Standard IFN plus ribavirin versus pegylated IFN plus ribavirin (Table 4 and Appendix 5, Figure 4b): A statistically significant impact on mortality could not be detected. One published trial[57] explicitly reported this outcome. Information for the other trial[58] was obtained from an FDA review.[56] Three deaths occurred among individuals in any treatment arm. The reasons for these are listed in Table 5.

Table 5: Number of and reasons for death in identified RCTs

Study	Duration After Enrolment in Trial	Patient Type	Treatment Arm	Description
Peg IFN alfa plus ribavirin trials				
Fried[57]	<72 weeks	Naïve	IFN alfa plus ribavirin	Male died after withdrawal from study because of hypertensive heart disease
Manns[56]	NR	Naïve	Peg IFN alfa plus ribavirin	Patient committed suicide
	NR	Naïve	IFN alfa plus ribavirin	Motor vehicle accident
IFN alfa plus ribavirin trials				
Davis[37] (2 trials)	36 weeks	Relapser	IFN alfa plus placebo	Woman with history of drug and alcohol abuse committed suicide
Lai[62]	196 weeks	Naïve	IFN alfa	Traffic accident
McHutchinson[38]	<24 weeks	Naïve	IFN alfa plus ribavirin	56-year-old male with history of diabetes, angina, hypertension and myocardial infarction secondary to hemolytic anemia
	<24 weeks	Naïve	IFN alfa plus placebo	59-year-old male with hypertension and diabetes had acute inferior wall and right myocardial infarction
	64 weeks	Naïve	IFN alfa plus placebo?	43-year-old male patient with history of illicit drug use and depression died of illicit drug overdose
	36 weeks	Naïve	IFN alfa plus ribavirin?	43-year-old female with history of "mild" depression died of an accidental overdose
Poynard[38]	NR	Naïve	IFN alfa plus ribavirin	Intracranial hemorrhage due to a fall during follow-up week 20

NR=not reported.

4.2.3 All-cause serious morbidity (non-fatal SAEs)

Standard IFN plus ribavirin versus IFN therapy alone (Appendix 5, Figure 2a): Rates of SAEs were available from 15.7% (8/51) of trials. Two reports mentioned this outcome. These trials included less than 30% of all patients. Based on these reports, meta-analysis did not reveal that combination therapy produced statistically different SAE rates (RR 1.02, 95% CI: 0.84 to 1.24) when compared with IFN therapy alone (Table 4). A breakdown of SAE rates in each treatment arm could not be produced using the available information. Supplementary information[38,92] indicated that the most commonly reported SAEs reported in the larger trials were psychiatric events (suicidal ideation, suicide attempt, anxiety, hallucination, depression, aggressive

reaction), gastrointestinal events (abdominal pain, vomiting), serious infection (pneumonia), cardiovascular events (myocardial infarction, angina, hypertension), anemia and thyroid disorder. There were three cases of hepatic carcinoma.[38,69]

Standard IFN plus ribavirin versus pegylated IFN plus ribavirin (Appendix 5, Figure 2b): Rates of SAEs were available from unpublished sources.[56,91] A significantly higher rate of non-fatal SAEs occurred in the pegylated IFN plus ribavirin combination therapy group compared with the IFN alfa-2b plus ribavirin control group (rate ratio=1.24, 95% CI: 1.01 to 1.51) during 48 weeks therapy and 24 weeks of follow-up (Table 4). Because the number of non-fatal SAEs experienced by each individual was unavailable, individual risk could not be calculated from these data. This effect was largely driven by serious infections (e.g., cellulitis, abcess, appendicitis) and SAEs experienced by less than 1% of the trial population (Table 6). Infrequent SAEs more commonly reported in both trials included attempted suicide, severe depression, psychosis, relapse of drug addiction, myocardial infarction, retinal thrombosis, gastroenteritis, fatigue, thyroid disorder, rheumatoid arthritis and aggravated psoriasis.

Table 6: Breakdown of SAE rates observed in pegylated IFN plus ribavirin RCTs

Serious Adverse Event (SAE)	**Incidence of SAEs (%)**		**Rate Ratio (95% CI)**
	Peg IFN alfa-2a or -2b plus ribavirin, n=1,519	IFN alfa-2b plus ribavirin, n=983	
Psychiatric event	50 (3.3)	29 (3.0)	1.12 (0.71, 1.76)
Serious infection	40 (2.6)	11 (1.1)	2.36 (1.21, 4.59)
Gastrointestinal event	30 (2.0)	23 (2.3)	0.84 (0.49, 1.45)
All other SAEs, each occurring in ≤1% of patients	168 (11.1)	76 (7.7)	1.43 (1.09, 1.88)

4.3 Secondary Outcomes

4.3.1 Withdrawals due to adverse events

To be classified as withdrawals due to death, adverse events or laboratory abnormalities, patients had to have received at least one dose of medication.

Standard IFN plus ribavirin versus IFN therapy alone (Appendix 5, Figure 3a)***:*** The likelihood of withdrawal from therapy due to one or several adverse events could be estimated from 59% (30/51) of trials. Compared to standard IFN alone, the relative risk of withdrawal due to one or several adverse events from standard IFN combined with ribavirin was 1.25 (95% CI: 1.03 to 1.52), equating with an absolute difference in risk of 2%. This implied that an extra patient would be required to withdraw due to adverse events after initiating therapy for every 50 treated with combination therapy compared with IFN alone.

Standard IFN plus ribavirin versus pegylated IFN plus ribavirin (Appendix 5, Figure 3b): A significant increase or decrease in withdrawals due to adverse events could not be detected (fixed effects estimate of RR 0.97, 95% CI: 0.75 to 1.24).

4.3.2 Quality of life

Standard IFN plus ribavirin versus IFN therapy alone: The effect of treatment on quality of life was not reported in any trial (0/51).

Standard IFN plus ribavirin versus pegylated IFN plus ribavirin: The effect of treatment on quality of life was not reported in published trials. An FDA summary[91] of one published trial[58] reported that health-related quality of life was assessed using a self-administered questionnaire. Details about the type of instrument used and the methods of administration were not supplied. Quality of life reportedly decreased during treatment and returned to baseline at the end of the post-treatment observation period, without significant differences detected between treatment arms.[56]

4.3.3 Virologic endpoints

Standard IFN plus ribavirin versus IFN therapy alone (Appendix 5, Figure 4a): Statistical heterogeneity was detected in the meta-analysis of viral response rates, but it was less when only those trials that enrolled IFN-naïve patients were pooled. The relative risk of not achieving a sustained virologic response was reduced by 27% (95% CI: 23 to 30) in these patients. In absolute terms, this meant that an additional patient avoided persistent viremia for every 4.6 (95% CI: 4.1 to 5.0) treated with standard IFN combined with ribavirin instead of standard IFN alone (Table 7).

Table 7: Effect of standard IFN plus ribavirin versus standard IFN therapy alone on virologic outcomes

Surrogate Outcome	Number of Trials	Sample Size	Relative Risk of not Achieving a Response (95% CI)	Statistical Heterogeneity	Absolute Risk Difference (95% CI)
Sustained Viral Response	31	4,574	0.75 (0.73 to 0.77)	$p<0.00001$ $X^2=206.45$ df=28	22% (20 to 24)
Naïve population only	7	2,443	0.73 (0.70 to 0.77)	$p=0.14$ $X^2=9.68$ df=6	23% (19 to 26)
End of Treatment Viral Response	46	6,047	0.72 (0.69 to 0.75)	$p<0.00001$ $X^2=206.45$ df=28	20% (18 to 23)
Naïve population only	12	3,083	0.70 (0.65 to 0.74)	$p=0.2$ $X^2=14.58$ df=11	21% (17 to 24)

Standard IFN plus ribavirin versus pegylated IFN plus ribavirin (Appendix 5, Figure 4b): The relative risk of not achieving a sustained viral response was reduced by 13% (RR 0.87, 95% CI: 0.80 to 0.94) in two trials. In absolute terms, this meant that an additional patient avoided persistent viremia for every 14 treated with pegylated IFN combined with ribavirin instead of standard IFN combined with ribavirin (Table 8).

Table 8: Effect of standard IFN plus ribavirin versus pegylated IFN plus ribavirin on virologic outcomes

Surrogate Outcomes	**Number of Trials**	**Sample Size**	**Relative Risk of not Achieving a Response (95% CI)**	**Absolute Risk Difference (95% CI)**
Sustained viral response, ITT population	2	2,502	0.87 (0.80 to 0.94)	7% (3 to 11)
Sustained viral response, Randomized and treated population	2	2,427	0.87 (0.80 to 0.94)	7% (3 to 11)
End of treatment viral response	2	2,502	0.75 (0.69 to 0.82)	12% (8 to 16)

5 DISCUSSION

We identified 53 unique RCTs in a systematic review. These RCTs described the treatment of adult patients with persistent, detectable viremia from HCV infection. Fifty-one unique randomized trials enrolling 7,474 patients compared the addition of ribavirin to IFN versus IFN by itself. Two additional randomized trials enrolling 2,729 patients for 72 weeks provided evidence of the effect of using pegylated IFN combined with ribavirin versus standard IFN and ribavirin. We re-examined these RCTs and conducted a meta-analysis to determine the incidence of death and serious morbidity, by analyzing the SAEs occurring during the clinical trials and withdrawals due to adverse events.

There were no detectable differences in the occurrence of death in any treatment arm. As death resulting from chronic HCV infection was measured in decades, it was not surprising that the reported rates of death in these short-term (six months to two years) trials were low. Deaths were accidental or related to established toxicities (e.g. suicide, anemia) from therapy.[92]

We discovered a significant increase in SAE rates from pegylated IFN plus ribavirin compared with standard IFN plus ribavirin, but a significant difference in withdrawal rates due to adverse events was not observed. This was unexpected, as increased serious morbidity would be expected to lead to increased withdrawal rates. Several explanations could account for this apparent contradiction, including latent SAEs occurring during follow-up, when withdrawal was no longer possible; a high baseline rate of withdrawal due to adverse events that were not life-threatening, such as fatigue or serious laboratory adverse events (e.g., neutropenia); or investigators' tolerance to side effects after greater experience.

The pattern of SAE and withdrawal rates seems to be in direct contrast when comparing standard IFN plus ribavirin versus IFN alone. We are not convinced about the strength of this finding because of a large proportion of unreported outcomes, but if it is true, it can be explained in several ways. This pattern may be related to the nature of SAEs encountered (e.g. anemia versus psychosis); it may reflect the trial protocol (e.g., stopping rules); or it may be a historical confounder (investigators were more comfortable with IFN and tended not to withdraw patients from studies when SAEs occurred).

We tried to minimize bias by basing our analysis on published and unpublished material[93] and by using two independent reviewers to abstract trial data. We combined data in accordance with published methods and looked for evidence of statistical heterogeneity across trials. We elected to use trial and patient characteristics identified a priori to explain heterogeneity and strengthen the validity of our findings.

One limitation of our analysis is that we did not conduct our own systematic literature review. The design of the original systematic reviews may have introduced a bias in the selection of RCTs, but reasonable efforts are made in the AHRQ's review to minimize this bias (e.g., prospective screening procedure with pre-defined selection criteria and more than one reviewer).

Another limitation of our analysis is that results relating to standard IFN combination therapy are not robust, because of a lack of information from randomized trial reports. For example, the rate of SAEs caused by the addition of ribavirin to standard IFN can only be estimated from two of 51 published trial reports (4%). In addition, the pooled result is driven almost solely from supplementary information and from one other trial. This rate is lower than a previously observed rate of safety reporting (30%).[94]

Even when outcomes are reported, how they are defined, monitored and collected is usually not reported. This leads to additional uncertainty. Further examination of the primary data is required to arrive at a reliable estimate of morbidity during treatment. It is necessary for manufacturers and regulatory bodies such as Health Canada to provide full disclosure of trial data or assessments of these data; this shortcoming is highlighted in our findings.[95]

We are aware of one published review that has tried to quantify mortality and serious morbidity through a meta-analysis of data from randomized controlled trials.[31] Unlike our analysis, however, only serious liver-related morbidity (histological cirrhosis assessed in a post-treatment liver biopsy, clinical cirrhosis as defined by the authors of the reports, hepatocellular carcinoma and liver transplantation) is analyzed. An analysis of serious morbidity from all causes is necessary to put these events into context.[96,97] As in their review, we discovered that most investigators did not report serious adverse outcomes.

Our findings regarding serious morbidity from pegylated IFN combination therapy are reflected in an FDA summary:[56] "The higher rates of SAEs and dose modification suggest the potential for greater toxicity of PEG-IFN and ribavirin compared to IFN and ribavirin."

Other more recent systematic reviews have quantified the rates of withdrawal due to adverse events. Our analysis is in general agreement with these findings.[30,33] Unlike our analysis, some reviews have also quantified the rates of treatment discontinuation from any cause (e.g., loss to follow-up, lack of efficacy).

6 HEALTH SERVICES IMPACT

Our findings have implications for patients, clinicians and policy makers. Clinicians and patients will need to decide if an increased chance of becoming serum-negative for HCV RNA is worth the short-term consequence of increased toxicity with pegylated IFN combination therapy.

Our findings also suggest that clinicians must make treatment decisions regarding standard IFN combination therapy based on limited reporting of death, SAE and withdrawal rates. Readers of this report should be cautious about interpreting findings that are based on a representative minority of trial reports and randomized patients. A more robust assessment can be made if unpublished data are added to the analysis.

Policy makers should be aware that increasing rates of serious and life-threatening events will require monitoring and that their management will increase costs and affect health service use in the short term.[98] Whether supporting this decision will save money in the long term will need to be considered through cost-effectiveness analysis that accounts for serious morbidity during treatment. Policy makers should consider that the adverse event and dropout rates seen in studies may be underestimates of what occurs in practice.[99,100] These findings are reflected in an FDA analysis:[91] "…therapy of patients with chronic hepatitis C is likely to be less rigidly controlled and more uneven outside of clinical trials. For these reasons the incidence of toxicities in the post-marketing phase may be higher than that observed in the clinical trial phase…"

Our analysis indicates that IFN-based therapies increase the probability of achieving a sustained viral response. This conclusion is reached in other systematic reviews.[30-32] Policy makers should note, however, that this purported benefit is an effect on an intermediate or surrogate outcome. While a higher sustained viral response rate may ultimately translate into reduced incidences of end-stage liver disease or hepatocellular carcinoma, this has not been proven.[101,102] An alternative interpretation of all the data suggests that no (or relatively little) such reduction may occur, so the cost of treatment (in terms of clinical gain) becomes prohibitively high.[103] Regardless, policymakers should expect to see the continued use and support of viral response measures in practice.

7 CONCLUSIONS

- Information on quantity or quality of life related to IFN-based treatment is lacking.
- Morbidity and mortality after therapy with ribavirin added to standard IFN could not be estimated from the randomized trial evidence.
- Pegylated IFN combined with ribavirin can increase the need for urgent medical attention when compared with standard IFN plus ribavirin.
- Pegylated IFN plus ribavirin therapy can reduce the risk of persistent viremia and liver enzyme elevation to the greatest degree, when it is compared with standard IFN plus ribavirin therapy or with standard IFN therapy alone.

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Appendix 1: PubMed Search to Identify Randomized Trials of Drug Therapy for Hepatitis C

Legend:

In PubMed:

[MeSH] = Medical Subject Headings, i.e. controlled subject vocabulary

[Title/Abstract Word] = Word occurs in the title or abstract field of the record

dt = drug therapy of a disease

In Dialog®

de = descriptor, ie. Medical Subject Heading (a controlled, thesaurus term)
dt = subheading for "drug therapy" of a disease
ae = subheading for "adverse effects"
to = sibheading for "toxicity"
ti = title (i.e. word has to occur in title field of the bibliographic record)
ab = abstract (ie word has to occur in abstract field of bibliographic record)
! = explode; picks up narrower terms as well, i.e. terms which are conceptually subsets of a broader term.
() = words must be adjacent
(w2) = words within the same field are within 2 words of each other
? = truncation symbol

DATABASE	LIMITS	KEYWORDS
PubMed	Performed August 21, 2001	1. hepatitis C, chronic/dt [MeSH term] 2. (clinical trials OR comparative study OR double-blind method OR random allocation) [MeSH term] 3. (clinical trial OR clinical trials OR random OR randomized OR randomised OR controlled trial OR controlled trials OR controlled clinical trials OR controlled clinical trial OR multicenter trial OR multicenter trials OR multicentre trial OR multicentre trials OR multi center trial OR multi center trials OR multi centre trial OR mutli centre trials OR meta analysis OR meta analyses OR metaanalysis OR metaanalyses OR meta-analysis OR meta-analyses OR research integration OR research overview OR research overviews OR quantitative review OR quantitative reviews OR quantitative overview OR quantitative overviews OR methodologic overview OR methodologic overviews OR methodologic review OR methodologic

		reviews OR systematic review OR systematic reviews OR integrative research OR quantitative synthesis OR comparative study OR comparative studies OR rct OR rcts OR single blind OR single blinded OR double blind OR double blinded OR triple blind OR triple blinded OR prospective study OR prospective studies OR retrospective study OR retrospective studies OR dummy OR sham OR treble blind OR treble blinded) [Title/Abstract word] 4. 1 AND (2 OR 3) 5. (IFN alfa-2a OR ribavirin){MeSH terms] 6. {IFN-a OR IFN alfa 2a OR ribavirin OR (PEG AND intron} OR roferon a OR infergen OR pegasys} [Title/Abstract words] 7. 1 AND (2 OR 3) AND (5 OR 6) ** No hits for IFN-a-NE OR IFN-a-SB OR pegylated IFN alfa-2a OR PEG Intron OR PEG-IFN-a-2B OR rebetrol as title/abstract words
Cochrane Collaboration and Update Software) Cochrane Library on CD-ROM	2001, Issue 2	1. hepatitis C, chronic [MeSH}= 163 Database of Reviews of Effectiveness = 3 (Abstracts of quality assessed systematic reviews) Controlled Clinical Trials Register = 146 References Health Technology Assessment Database = 2 abstracts (INAHTA or other healthcare technology agency) NHS Economic Evaluation Database = 12 (Abstracts of economic evaluation of health care interventions)
"CCOHTA HTA Checklist"	August 2001	Websites of health technology assessment and other agencies, specialized databases (NHS Centre for Reviews and Dissemination, trial registries, etc.)

Appendix 2: Literature Search for Safety Information

DATABASES	LIMITS	KEYWORDS
Dialog® OneSearch® MEDLINE® (File 155) TOXLINE® (File 156)	1992+ (Performed March 12, 2002)	1. IFN-alpha!(l)ae,to 2. ribavirin/ae,to 3. Set 1 AND Set 2 4. IFN-alpha! AND ribavirin/de 5. [adverse(w)drug()event? OR adverse(w)event? OR safety OR safe OR morbidity OR mortality]/ti,ab OR mortality! OR fatal outcome/de OR morbidity/de OR safety! 6. Set 4 AND Set 5 7. [IFN(w)a OR IFN(w)alfa OR IFN(w)alpha OR roferon]/ti,ab 8. [rebetol OR ribavirin]/ti,ab 9. Set 5 AND Set 7 AND Set 8 10. rebetron/ti,ab AND Set 5 11. Set 3 OR Set 6 OR Set 9 OR Set 10 12. hepatitis c, chronic/de 13. chronic(w)hepatitis(w)c/ti,ab 14. Set 12 OR Set 13 15. Set 11 AND Set 14 16. dt = (clinical trial OR clinical trial, phase i OR clinical trial, phase ii OR clinical trial, phase iii OR clinical trial, phase iv OR meta-analysis OR controlled clinical trial OR randomized controlled trial OR multicenter study OR review OR review literature OR review, multicase OR review of reported cases) 17. clinical trials! OR review literature! OR cohort studies!) 18. (double-blind method OR random allocation OR meta-analysis)/de 19. [(random? OR controlled()trial? OR controlled()clinical() trial? OR clinical()trial? OR double()blind?]/ti,ab 20. (multicent? trial? OR multi cent? trial? OR meta analy? OR metaanaly? OR meta-analysis)/ti,ab 21. [research()integration OR research() overview? OR quantitative()review? OR quantitative()overview? OR methodologic() review? OR methodologic()overview?]/ti,ab 22. [systematic()overview? OR

		systematic()review? OR integrative()research OR quantitative()synthesis OR comparative()stud? OR prospective()stud? OR retrospective()stud? OR single()blind? OR triple()blind? OR treble()blind? OR dummy OR sham OR rct? OR case(w)control?(w)series OR case(w)control?(w)stud? OR case(w)series OR case(w)cohort? OR observational(w) cohort?)]/ti,ab 23. Set 16:22 24. Set 15 AND Set 23 25. Set 24/1992:2002 26. Set 25 from 155 27. Set 25 from 156
EMBASE (File 72)		28. IFN alpha(l)ae,to OR IFN alpha 2a(l)ae,to OR IFN alpha 2b(l)ae,to 29. ribavirin(l)ae,to 30. Set 28 AND Set 29 31. (IFN alpha OR IFN alpha 2a OR IFN alpha 2b) AND ribarivin/de 32. (drug safety OR morbidity OR mortality OR drug fatality OR fatality OR drug toxicity)/de OR [adverse(w)drug()event? OR adverse(w)event? OR safety OR safe OR morbidity OR mortality]/ti,ab 33. Set 31 AND Set 32 34. [IFN(w)a OR IFN(w)alfa OR IFN(w)alpha OR roferon]/ti,ab 35. [rebetol OR ribavirin]/ti,ab 36. Set 34 AND Set 35 AND Set 32 37. (rebetron/ti,ab OR rebetron/de OR tn=rebetron) AND Set 32 38. Set 30 OR Set 33 OR Set 36 OR Set 37 39. hepatitis c/de AND chronic disease/de 40. Set 39 OR Set 13 41. Set 38 AND Set 40 42. controlled study! OR (comparative study OR randomized controlled trial OR prospective study OR retrospective study OR meta analysis OR clinical trial OR multicenter study OR phase 1 clinical trial OR phase 2 clinical trial OR phase 3 clinical trial OR phase 4 clinical trial OR case control study OR cohort analysis OR double blind procedure OR single blind procedure)/de

		43. Set 42 OR Set 19 OR Set 20 OR Set 21 OR Set 22 44. Set 41 AND Set 43 45. Set 44/1992:2002 46. Set 45 from 72
Biosis Previews® (File 5)		47. [IFN(w)alfa OR IFN(w)alpha OR IFN(w)a OR roferon]/ti,ab 48. ribavirin/na OR ribavirin/de OR ribavirin/ti,ab OR rebetol/ti,ab 49. Set 47 AND Set 48 50. rebetron/na OR rebetron/ti,ab 51. Set 49 OR Set 50 52. (adverse drug reactions OR adverse drug effects OR safety OR drug safety OR morbidity OR morbidity rate/de 53. adverse(w)drug()event? OR adverse(w)event? OR safety OR safe OR morbidity OR mortality OR fatality OR fatal(w)outcome?]/ti,ab 54. Set 52 OR Set 53 55. Set 51 AND Set 54 56. (chronic hepatitis c OR chronic hepatitis c infection OR chronic hepatitis c virus infection)/de OR chronic()hepatitis()c/ti,ab 57. Set 55 AND Set 56 58. clinical trial OR randomized trial OR prospective study OR randomized controlled trial OR multicenter study OR randomized clinical trial OR case-control study)/de 59. Set 58 OR Set 19 OR Set 20 OR Set 21 OR Set 22 60. Set 57 AND Set 59 61. Set 60/1992:2002 62. Set 61 from 5
		63. Set 26 OR Set 27 OR Set 46 OR Set 62
		64. Rd (Reduce duplicates) Set 63 = 132 unique references
		65. Type Set 64/all from 155, 156, 72, 5

Appendix 3: Data Abstraction Form for Direct Estimates of Outcomes from Trial Reports

Use one form per report.
Date _____ Reviewer's initials _____
Reference manager number _____
Study title _____
Other references or trials that may link with this study _____

Detailed Follow-up Information				
Treatment arms				
Number of patients	Screened			
	Eligible			
	Randomized			
	Evaluable			
Number of patients followed-up at end of study				
Reasons for no follow-up (total)				
Missed assessment or visit				
Lost to follow-up				
Patient's request				
Non-compliance				
Gross violation of inclusion or exclusion criteria				
Other (excluding death)				
Death				

Outcomes			
Treatment arms			
Number (ITT)			
Number of deaths			
Number of patients with SAEs*			
Number of SAEs†			
Number of patients withdrawn from study because of adverse events†:			
Total number of patients with adverse events†			
Total number of adverse events†			
Number of laboratory-determined adverse events†			

*irrespective of association with treatment; and includes deaths and patients withdrawn from study or treatment because of SAEs; †irrespective of association with treatment; ITT=intention to treat.

Appendix 4: Characteristics of RCTs Identified for Inclusion in Review

Trial, Setting, Design, Number of Patients	Experience with IFN	Patients' Characteristics	Relevant Comparators	Treatment Duration in Weeks	Follow-up in Weeks	Outcomes (Mortality, Morbidity, Adverse Events, Quality of Life) Reported	Other Outcomes	Comments
Standard IFN plus ribavirin versus IFN therapy alone								
Andreone 1999a[68] Italy R UB n=32	No ALT response after 5 months IFN	HCV-RNA+, elevated ALT, biopsy+	IFN alfa-n3 (6 MU tiw) IFN alfa-n3 (6 MU tiw) plus ribavirin (400 mg bid)	16	24	WDAEs	Biochemical (ALT) ETR; viral ETR; composite outcome of both	Pilot study involving third arm (ketoprofen)
Andreone 1999b[69] Italy R UB n=40	No ALT response with 6 months IFN therapy ≥12 months prior	HCV-RNA+, elevated ALT, biopsy+	IFN alfa-n3 (3 MU tiw) IFN alfa-n3 (3 MU tiw) plus ribavirin (400 mg bid)	24	24	SAEs, WDAEs	Biochemical (ALT) ETR; viral ETR; SBR; SVR	
Ascione[40] (abstract) Italy R UB n=20	"Non-responders" to previous IFN	HCV-RNA+, elevated ALT, biopsy+	IFN alfa-n3 (3 MU tiw) IFN alfa-n3 (3 MU tiw) plus ribavirin (500 mg bid)	24	24		Biochemical ETR; biochemical SR	IFN alfa-n3 (3 MU tiw) for 6 months if ETR
Barbaro 1998[70] Italy R UB MC n=303	No ALT and viral response to 12 weeks IFN alfa-2b (>3 months and <6 months before enrolment)	HCV-RNA+, elevated ALT	IFN alfa-2b (6 MU tiw) IFN alfa-2b (3 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	24	24	WDAE quantified	Biochemical (ALT) and viral ETR and SRs	Relapsers excluded

Barbaro 1999[39] Italy R UB MC n=400	No ALT and viral ETR to 24 weeks IFN 3 MU (>3 months and <6 months before enrolment) or ETR with relapse <12 weeks after treatment	HCV-RNA+, biopsy+	IFN alfa-2b (6 MU tiw) IFN alfa-2b (3 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	24	24	WDAE described	Biochemical (ALT) and viral ETR and SRs, histology	Relapsers and non-responders stratified into two groups
Barbaro 2000[59] Italy R UB MC n=428	Naïve	HCV-RNA+, biopsy+ (within 1 year), elevated ALT	IFN alfa-2b (3 MU tiw) IFN alfa-2b (3 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	48 24	24	SAEs described	Biochemical (ALT) and viral ETR and SRs	
Bell[71] Norway R UB MC n=53	No SVR to 24 weeks IFN alfa-2a (3 MU tiw x24 weeks or 6 MU tiw x12 weeks then 3 MU tiw x3 weeks) ≥12 months prior	HCV-RNA+, elevated ALT	IFN alfa-2a (4.5 MU tiw) IFN alfa-2a (4.5 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	24	24	WDAEs	Biochemical (ALT) and viral ETR and SRs	Relapsers and non-responders stratified
Bellobuono 1997[88] Italy R UB n=48	No ALT response or ALT relapse after one to two courses of IFN alfa-2a, IFN alfa-2b, IFN alfa-n or IFN alfa-n3 therapy	HCV+, elevated ALT ≤6 months before trial	IFN alfa-n3 (3 MU tiw <60 kg or 6 MU tiw ≥60 kg) IFN alfa-n3 (3 MU tiw <60 kg or 6 MU tiw ≥60 kg) plus ribavirin (500 mg bid) IFN alfa-2b (5 MU tiw) plus ribavirin (500 mg to 600 mg bid)	24	24	WDAEs	Biochemical (ALT) and viral ETR and SRs	Relapsers and non-responders stratified

Bellobuono 1999[55] Italy R UB n=60	Relapsers to IFN alfa	HCV-RNA+, elevated ALT biopsy +	IFN alfa-2b (5 MU tiw) IFN alfa-2b (5 MU tiw) plus ribavirin (500 mg to 600 mg bid)	48	24		Biochemical (ALT) and viral ETR and SRs	
Bellobuono 2000[72] Italy R UB n=48	No response to 4 weeks IFN alfa-2b (3 MU tiw)	HCV-RNA+, biopsy+, elevated ALT (>1.5x normal)	IFN alfa-2b (6 MU tiw) IFN alfa-2b (3 MU tiw) plus ribavirin (500 mg bid)	44	24	WDAEs	Biochemical (ALT) and viral ETR and SRs	
Berg[41] (abstract) Germany R UB n=64	Naïve	HCV-RNA+, biopsy+	IFN alfa (6 MU tiw) IFN alfa (6 MU tiw) plus ribavirin (14 mg/kg/day)	12			Viral ETR, viral kinetics	Kinetics study
Berg 2000[84] Germany R UB MC n=185	Previously naïve patients with no viral ETR from 12 weeks IFN alfa (6 MU tiw) or IFN alfa (6 MU tiw) plus ribavirin (14 mg/kg/day)	HCV-RNA+, elevated ALT, biopsy+	IFN (3 MU tiw) No treatment	40	24	WDAEs	Biochemical (ALT) and viral ETR and SRs	
Bresci[73] Italy R UB n=100	No ALT and viral response to 16 weeks IFN alfa-2b (3 MU tiw)	HCV+, biopsy+ elevated ALT ≤6 months before trial	IFN alfa (6 MU tiw) IFN alfa (6 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	24	48		Biochemical (ALT) and viral ETR and SRs	Discontinuation due to anemia reported only

Brillanti[86] Italy R UB n=30	No ALT and viral ETR to 24 weeks IFN alfa-n3 (3 MU tiw) ≥12 months prior or ETR with relapse <12 weeks after treatment ≥12 months prior	HCV+, biopsy+ elevated ALT, no antibodies to IFN	IFN alfa-n3 (3 MU tiw) IFN alfa-n3 (3 MU tiw) plus ribavirin 400 mg bid	24	24		Biochemical (ALT) and viral ETR and SRs	Responders and relapsers stratified
Bugliescu[42] (abstract) Romania R UB n=38	"Non-responders" and "relapsers" to previous IFN therapy	HCV-RNA+, elevated ALT, biopsy+	IFN alfa (3 MU tiw) IFN alfa (3 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	IFN: 48 IFN: 48 Ribavirin: 24			Biochemical (ALT), viral and histological ETR	
Caremani[43] (abstract) Italy R UB n=36	Relapse from 48 weeks IFN alfa-2b or IFN alfa-n (3 MU tiw)	Biopsy+, "chronic hepatitis C"	IFN alfa-n3 (3 MU tiw) IFN alfa-n3 (3 MU tiw) plus ribavirin 80 mg daily	24	24		Viral and biochemical SR (composite), histology	
Cavalletto[85] Italy R UB n=100	No ALT and viral ETR to at least 24 weeks IFN alfa (3 MU tiw) ≥8 months prior or ETR with ALT relapse after treatment cessation	No ALT ETR from 8 weeks IFN alfa (6 MU tiw)	IFN alfa-n (3 MU tiw) IFN alfa-n (3 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	24	24		Biochemical (ALT), viral ETR and SR	Four randomized comparisons

Chapman[83] UK R UB MC n=32	ALT (1.5x upper limit) and viral relapse after 24 weeks IFN alfa (3 MU tiw)	Biopsy+, HCV+, ALT elevated	IFN alfa-2a (6 MU tiw) followed by IFN alfa-2a (3 MU tiw)	Monotherapy: 24 weeks high dose followed by 24 weeks regular dose	24	WDAE	Biochemical and virological SR	Startified for cirrhosis
			IFN alfa-2a (3 MU tiw) plus ribavirin (1,000 mg per day)	Combination: 24 weeks of IFN and 12 weeks of ribavirin				
Chemello[60] Italy R UB n=30	Naïve	HCV-RNA+, biopsy+	IFN alfa-n3 (3 MU tiw)	24	48	SAE, WDAE	Biochemical and virological ETR, SR	Third "ribavirin only" treatment arm
			IFN alfa-n3 (3 MU tiw) plus ribavirin 15 mg/kg daily					
Davis[37] International (France, Germany, Spain, US) R DB MC n=345	ALT relapse within 12 months of >20 weeks but ≤72 weeks IFN alfa-2a, IFN alfa-2b or IFN alfa-n1 (3 MU to 6 MU tiw)	HCV-RNA+, elevated ALT, biopsy+	IFN alfa-2b (3 MU tiw) plus placebo	24	24	Mortality, SAE, WDAEs	Biochemical and virological ETR, SR, histology	Industry-sponsored "relapse" study., high methodological quality
			IFN alfa-2b (3 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)					

de Lédinghen[44] (abstract) France R UB MC n=390	"Non-responders" to previous IFN therapy	HCV-RNA+, elevated ALT	IFN alfa-2b (6 MU tiw then 3 MU tiw)	High dose IFN 24 weeks followed by low dose IFN 24 weeks			12-week biochemical and viral TR	Interim analysis
			IFN alfa-2b (6 MU tiw then 3 MU tiw) plus ribavirin 500 mg bid	High dose IFN 24 weeks followed by low dose IFN 24 weeks ribavirin 48 weeks				
			IFN alfa-2b (3 MU tiw then 3 MU tiw) plus ribavirin 500 mg bid	48				
el-Zayadi[61] Egypt R UB n=52	Naïve	HCV-RNA+, elevated ALT, biopsy+	IFN alfa-2b (3 MU tiw)	24	24	WDAE	Biochemical and virological ETR, SR, histology	Genotype 4 virus study
			IFN alfa-2b plus ribavirin (500 mg bid)					
Ferenci[74] Austria R UB MC n=157	No ALT and viral response to 12 weeks IFN alfa-2b (5 MU tiw)	HCV-RNA+, elevated ALT	IFN alfa-2b (5 MU q2w followed by 10 MU q2w if no 12 week viral response)	24	24	WDAE	Biochemical and virological ETR, SR	
			IFN alfa-2b (5 MU q2w followed by 10 MU q2w if no 12 week viral response) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)					

Gerotto[75] Italy R UB n=15	"No" sustained response" to IFN monotherapy and second cycle of monotherapy or combination therapy with ribavirin. All were given IFN alfa therapy for 2 months prior		IFN alfa (6 MU tiw) IFN alfa (6 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	24			Viral ETR	All patients HCV genotype 1a or HCV genotype 1b; a genotype analysis more than a study of clinical effectiveness.
Gross[45] (abstract) US R DB MC n=69	Naïve	HCV-RNA+, elevated ALT, biopsy+ within 2 years	IFN afa-2b (5 MU tiw) plus placebo IFN alfa-2b (5 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	24		WDAE	Biochemical and viral ETR	Interim results: patients with resistance at 24 weeks scheduled to continue 28 weeks treatment
Khakoo[89] UK R UB n=24	Naïve or relapsed to prior IFN treatment	HCV-RNA+, elevated ALT (if available), biopsy+ (recent)	IFN alfa-2b (3 MU qw for first week followed by tiw) IFN alfa-2b plus ribavirin 600 mg	6	4	WDAE	Biochemical and viral ETR	Pharmacokinetic study: third "ribavirin only" trial arm; information on number of naïve versus relapse in each trial arm not given although most patients IFN naive
Koshy[90] Kuwait R UB n=112	NR	HCV-RNA+, elevated ALT (>1.5x upper limit of normal), biopsy+ without cirrhosis	IFN alfa-2b (5 MU tiw) IFN alfa-2b (5 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	24	24	WDAE	Biochemical and virological ETR, SR	HCV genotype 4

Lai[62] Taiwan R UB n=60	Naïve	anti-HCV+, elevated ALT, biopsy+	IFN alfa-2a (3 MU tiw)	24	96	Mortality, WDAE	Biochemical and virological ETR, SR	
			IFN alfa-2a (3 MU tiw) plus ribavirin 400 mg tid					
Mangia[63] (abstract) Italy R UB n=200	Naïve	Elevated ALT for 6 months, HCV-RNA+, biopsy+ within 6 months	IFN alfa (5 MU tiw)	48	24	WDAE	Biochemical and viral ETR, SR	Published in abstract form previously
			IFN alfa (5 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)					
Marcellin[46] (abstract) France R B MC n=100	Relapse after 24 to 48 weeks IFN alfa (3 MU tiw)		IFN alfa-2a (4.5 MU tiw) plus placebo	24	24		Viral ETR and SR	
			IFN alfa-2a (4.5 MU tiw) plus ribavirin 500 mg bid					
McHutchinson[64] US R DB MC n=912	Naïve	HCV-RNA+, biopsy+ within 1 year, elevated ALT for 6 months	IFN alfa-2b (3 MU tiw) plus placebo	48	24	WDAE	Biochemical and viral ETR, SR, histology	Supplementary data available
			IFN alfa-2b (3 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	24				
			IFN alfa-2b (3 MU tiw) plus ribavirin (500 mg bid >75 kg, 600 mg bid >75 kg)	48				

Milella[76] Italy R UB n=88	No response or relapse after minimum 6 months IFN alfa 6 MU tiw ≥6 months and ≤12 months before enrolment	HCV-RNA+, elevated ALT for 6 months, biopsy+ within 6 months, no anti-IFN abs	IFN alfa-n (6 MU tiw) IFN alfa-n (6 MU tiw) plus ribavirin (500 mg bid)	24	48	WDAE	Biochemical and viral ETR, SR	
Nunes[47] (abstract) US R DB n=122	"Non-responders" and "relapsers" in patients who "had previously failed IFN monotherapy"		IFN alfa (3 MU tiw) IFN alfa (3 MU tiw) plus ribavirin (500 mg bid)	8			Viral ETR	Extends into open-label crossover analysis at 6 months
Pawlotsky[48] (abstract) Israel, France, US R UB n=28	NR	HCV-1b+	No treatment IFN alfa-2b (3 MU qd) IFN alfa-2b (3 MU tiw) IFN alfa-2b (3 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	12			HCV-RNA levels	HCV kinetics study

Pol 1999[77] France R UB MC n=126	No ALT or viral response to ≥12 weeks IFN alfa-2a or IFN alfa-2b	HCV-RNA+, elevated ALT, biopsy+	IFN alfa-2b (6 MU tiw then 3 MU tiw)	High dose IFN 24 weeks followed by low dose IFN 24 weeks	24	WDAE	Biochemical and viral ETR and SR	
			IFN alfa-2b (6 MU tiw then 3 MU tiw) preceded by 8 weeks ribavirin 500 mg bid followed by additional 8 weeks ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	High dose IFN 24 weeks followed by low dose IFN 24 weeks ribavirin 16 weeks as described				
Pol 2000[65] France R UB MC n=346	Naïve	HCV-1b+	IFN alfa-2b 6 MU tiw followed by 3 MU tiw	High dose IFN 24 weeks followed by 24 weeks low dose IFN	24	WDAE	Biochemical and viral ETR and SR	
			IFN alfa-2b 10 MU tiw followed by 6 MU tiw	High dose IFN 24 weeks followed by 24 weeks low dose IFN				
			IFN alfa-2b 6 MU tiw followed by 3 MU tiw plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	High dose IFN 24 weeks followed by 24 weeks low dose IFN, ribavirin: stratified to 16, 24 and 48 weeks				

Portal[49] (abstract) France R UB MC n=297	"Relapsers" to previous IFN therapy who then respond to 24 weeks therapy	HCV-RNA+, elevated ALT, biopsy+	IFN alfa-2b 6 MU tiw followed by 3 MU tiw	24 weeks +24 weeks	24		Biochemical and viral ETR and SR	Stratified according to initial viremia
			IFN alfa-2b 6 MU tiw followed by 3 MU tiw plus ribavirin 600 mg daily	IFN 24 weeks +24 weeks, ribavirin 24 weeks				
			IFN alfa-2b 6 MU tiw followed by 3 MU tiw plus ribavirin 600 mg daily	IFN 24 weeks +24 weeks, ribavirin 48 weeks				
Poynard[66] International (France, Canada, Germany, Sweden, Italy, UK, Australia, Israel, Greece, Switzerland, Portugal, Spain) R B MC n=832	Naïve	HCV-RNA+, biopsy+ within 12 months, elevated ALT for 6 months	IFN alfa-2b (3 MU tiw) plus placebo	48	24	WDAE	Biochemical and viral ETR and SR, histology	
			IFN alfa-2b (3 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	24				
			IFN alfa-2b (3 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	48				
Reichard[67] Sweden R DB MC n=100	Naïve	HCV-RNA+, biopsy+ within 12 months, elevated ALT for 6 months	IFN alfa-2b (3 MU tiw) plus placebo	24	24	WDAE	Biochemical and viral ETR and SR, histology	High quality study
			IFN alfa-2b (3 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)					

Ricchiuti[50] (abstract) Italy R UB n=50	Naïve, IFN alfa-2b 6 MU tiw for 4 weeks before enrolment	"Chronic hepatitis C"	IFN alfa-2b (6 MU tiw)	20			Biochemical and viral ETR	
			IFN alfa-2b (6 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)					
Salmerón[87] Spain R UB n=62	Relapsers (ALT response at end of therapy but increased during follow-up) or non-responders (ALT did not normalize) with IFN	HCV-RNA+, elevated ALT, biopsy+	IFN alfa-2b (3 MU tiw)	24	72		Biochemical and viral ETR and SR	
			IFN alfa-2b (3 MU tiw) plus ribavirin 600 mg daily					
Sarin[51] (abstract) India R UN n=22	NR	"Chronic hepatitis", biopsy+	IFN alfa-2b 3 MU tiw	48 weeks	24	SAE	Biochemical and viral ETR and SR	All patients with cirrhosis; non-CHC-related cirrhosis patients also randomized
			IFN alfa-2b 3 MU tiw plus ribavirin 400 to 600 mg bid	IFN 48 weeks, ribavirin 24 weeks				
Scotto[78] Italy R UB n=20	Non-responder (no ALT normalization) to IFN alfa-2b (3 MU tiw for 24 weeks) at least 12 months previous	anti-HCV, elevated ALT (5-fold increase ≥6 months), biopsy+	IFN alfa-n (3 MU tiw) i.m. plus	24	24		Biochemical and viral ETR and SR	Title indicates this is a "pilot study"
			IFN alfa-n (3 MU tiw) i.m. plus ribavirin 800 mg daily for 8 weeks then IFN alfa-n (3 MU tiw) i.m. for 16 weeks	24				

Shiffman[79] US R UB MC n=140	Non-responder (HCV-RNA+ within 2 weeks of completing prior course; if HCV-RNA unknown, no ALT response during or at end of treatment) to ≥3 months and ≤18 months IFN alfa-2b (maximum 3 MU tiw), IFN alfa-2a (maximum 6 MU tiw) or IFN alfacon-1 (9 mcg tiw)	HCV-RNA+; elevated ALT;	IFN alfa-2b 5 MU tiw IFN alfa-2b 3 MU tiw plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	12	N/A		Biochemical and viral ETR	This study attempts to evaluate various treatment "strategies" but does not allow for causal evaluations or simple comparisons as randomization is destroyed after 12 weeks
Sostegni[80] Italy R UB n=96	Non-responders (no ALT or viral response) to ≥12 weeks IFN alfa 3 MU tiw	HCV-RNA+, biopsy+, elevated ALT (>1.5 times upper limit of normal)	IFN alfa-n3 (3 MU tiw) IFN alfa-n3 (3 MU tiw) plus ribavirin 500 mg bid Ribavirin 500 mg bid for 24 weeks followed by IFN alfa-n3 (3 MU tiw) for 24 weeks	24 24 48	24	WDAE	Biochemical and viral ETR and SR and histology	

Taliani[54] (abstract) Italy R UB n=52	Naïve	"HCV chronic patients"	IFN alfa (6 MU tiw) IFN alfa (3 MU 6 days/week) IFN alfa (3 MU 6 days/week) plus (500 mg bid <75 kg, 600 mg bid >75 kg)	24			Biochemical and viral ETR	Viral kinetics study
Toccacelli[81] Italy R UB n=24	Non-responders (no ALT response to IFN alfa-n3 3 MU tiw for 6 months)	HCV-RNA+, elevated ALT for last 6 months, biopsy+	IFN alfa-n3 (3 MU tiw) IFN alfa-n3 (3 MU tiw) plus ribavirin 400 mg bid	24	24	WDAE	Biochemical and viral ETR and SR	
Tripi[82] Italy R UB MC n=72	Non-responders (not defined) to ≥2 courses IFN alfa-n 6 MU tiw for ≥16 weeks >6 months before enrolment	HCV-RNA+, elevated ALT, biopsy+	IFN alfa-n3 (6 MU tiw) IFN alfa-n3 (6 MU tiw) plus ribavirin 1,200 mg i.m.	24	24	WDAE	Biochemical and viral ETR and SR	HCV genotype 1a (n=5), 1b (n=50), 2a (n=8)
Vandelli[53] (abstract) Italy R UB n=98	Non-responders to prior therapy (486 MU total dose of IFN alfa)	"Chronic hepatitis C"	IFN alfa-2b (6 MU daily) for 4 weeks followed by 6 MU every other day IFN alfa-2b (6 MU daily) for 4 weeks followed by 6 MU every other day plus ribavirin 14 mg/kg daily	48			Biochemical and viral ETR	

Wood[52] (abstract) US R UB n=not described	Non-responders (no viral ETR to ≥20 weeks of IFN (3 to 5 MU tiw)	"Chronic hepatitis C"	IFN alfa 10 MU daily for 10 days then IFN alfa 5 MU daily for 74 days then 5 MU tiw for 24 weeks IFN alfa 10 MU daily for 10 days then ribavirin 500 mg bid combined with IFN alfa 5 MU daily for 74 days then ribavirin 500 mg bid combined with 5 MU tiw for 24 weeks	36				Interim analysis of 26 patients
Standard IFN plus ribavirin versus pegylated IFN plus ribavirin								
Manns[58] International (Austria, France, Germany, Greece, Spain, Switzerland, UK, US) R UB MC n=1,530	Naïve	HCV RNA+, elevated ALT (above upper limit of normal), biopsy+ within 12 months;	Peg IFN alfa-2b (1.5 mcg/kg qw) plus ribavirin 400 mg bid Peg IFN alfa-2b (1.5 mcg/kg qw) for 4 weeks then peg IFN alfa-2b (0.5 mcg/kg qw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg) IFN alfa-2b (3 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	48	24		Biochemical and virological ETR and SR	Mortality, SAE and WDAE information available from FDA web site

Fried[57] International (Australia, Brazil, Germany, Italy, Mexico, Spain, Taiwan, US) R PB MC n=1,121	Naïve	HCV-RNA+, elevated ALT (above upper limit of normal), biopsy+	Peg IFN alfa-2a (180 mcg qw) plus placebo Peg IFN alfa-2a (180 mcg qw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg) IFN alfa-2b (3 MU tiw) plus ribavirin (500 mg bid <75 kg, 600 mg bid >75 kg)	48	24	Mortality, WDAE	Biochemical and virological ETR and SR	Treatment arms with placebo and ribavirin blinded

MU=million units; tiw=three times weekly; elevated alamine trasaminase enzyme (ALT) defined as at least twice the upper limit of normal unless otherwise stated; R=randomized; UB=unblinded; MC=multicentre; IFN alfa-n=natural IFN; IFN alfa-n3=leukocytic IFN alfa; ETR=end of treatment response; WDAE=withdrawls due to adverse events; SBR=sustained biochemical response; Qd=daily; abs=antibodies; qw=once weekly; q2w=twice weekly; NR=not reported; TR=treatment response; bid=twice daily; SVR=sustained viral response; SR=sustained response; DB=double-blinded; UB=unblinded; N/A=not available; PB=patient blinded; MC=multicentre; mcg=microgram; MU=million units; i.m.=intramuscularly

Appendix 5: Forest Plots for Meta-analysis of Outcomes

Any death occuring during treatment or at follow-up was recorded.

Figure 1a: All-cause mortality (fatal SAEs),
standard IFN plus ribavirin compared to IFN alone

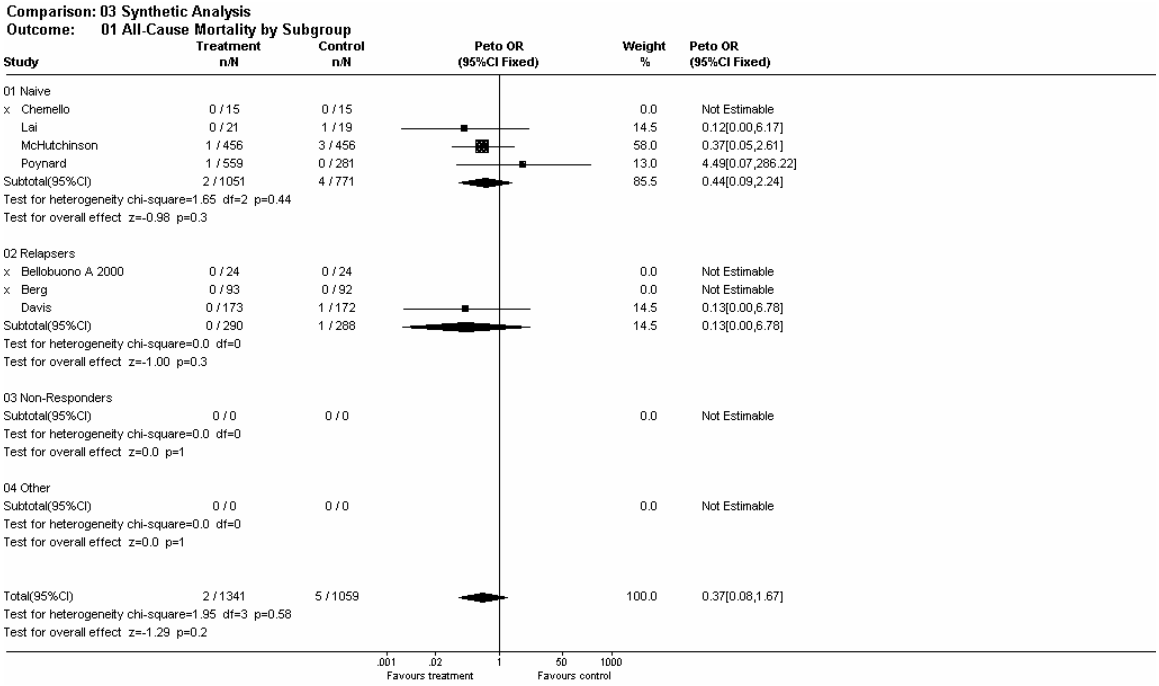


Figure 1b: All-cause mortality (fatal SAEs),
pegylated IFN plus ribavirin compared to IFN plus ribavirin

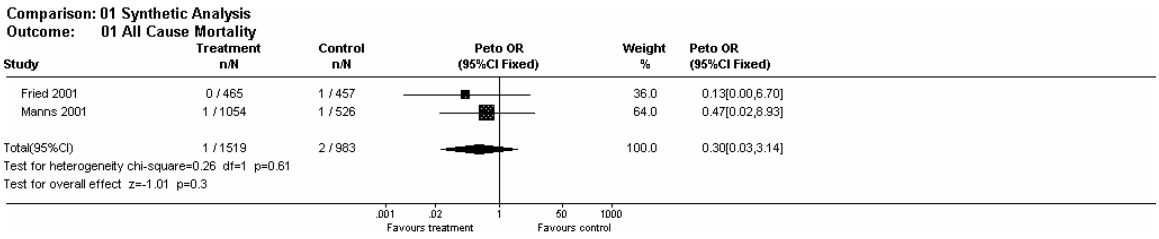


Figure 2a: All-cause morbidity (non-fatal SAE rates), standard IFN plus ribavirin compared to IFN alone

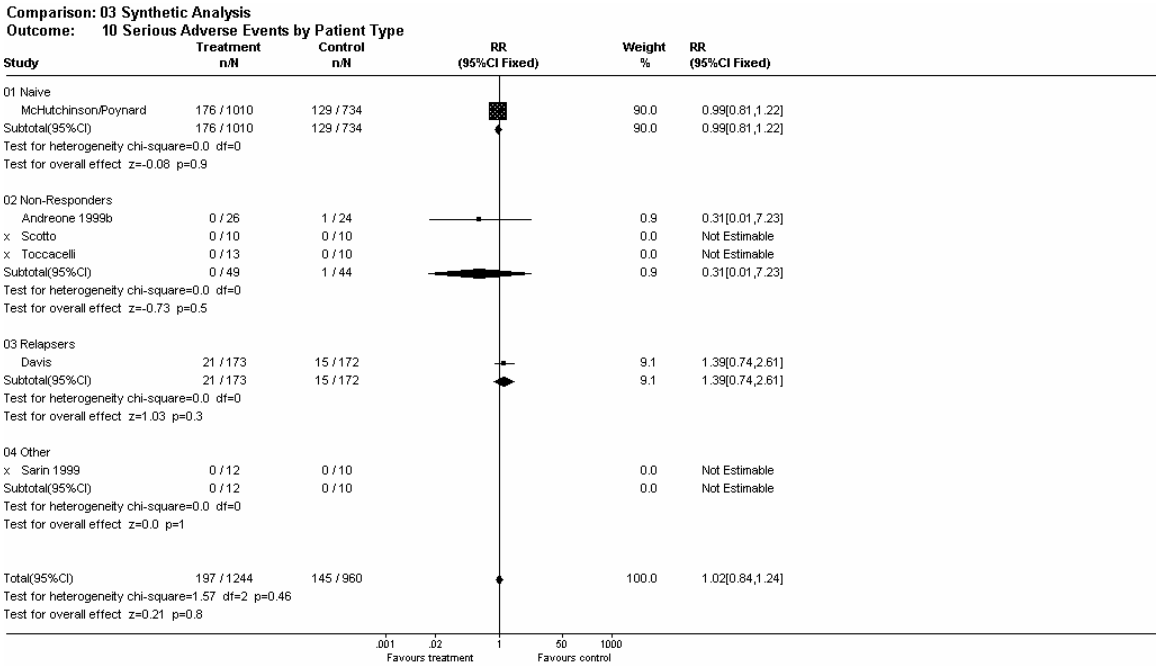


Figure 2b: All-cause morbidity (non-fatal SAE rates), pegylated IFN plus ribavirin compared to IFN plus ribavirin

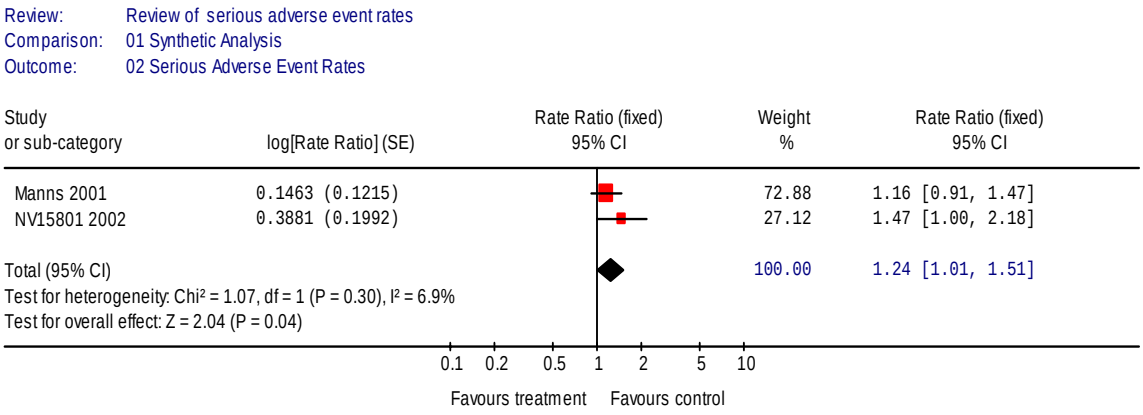


Figure 3a: Withdrawals due to adverse events, standard IFN plus ribavirin versus IFN alone

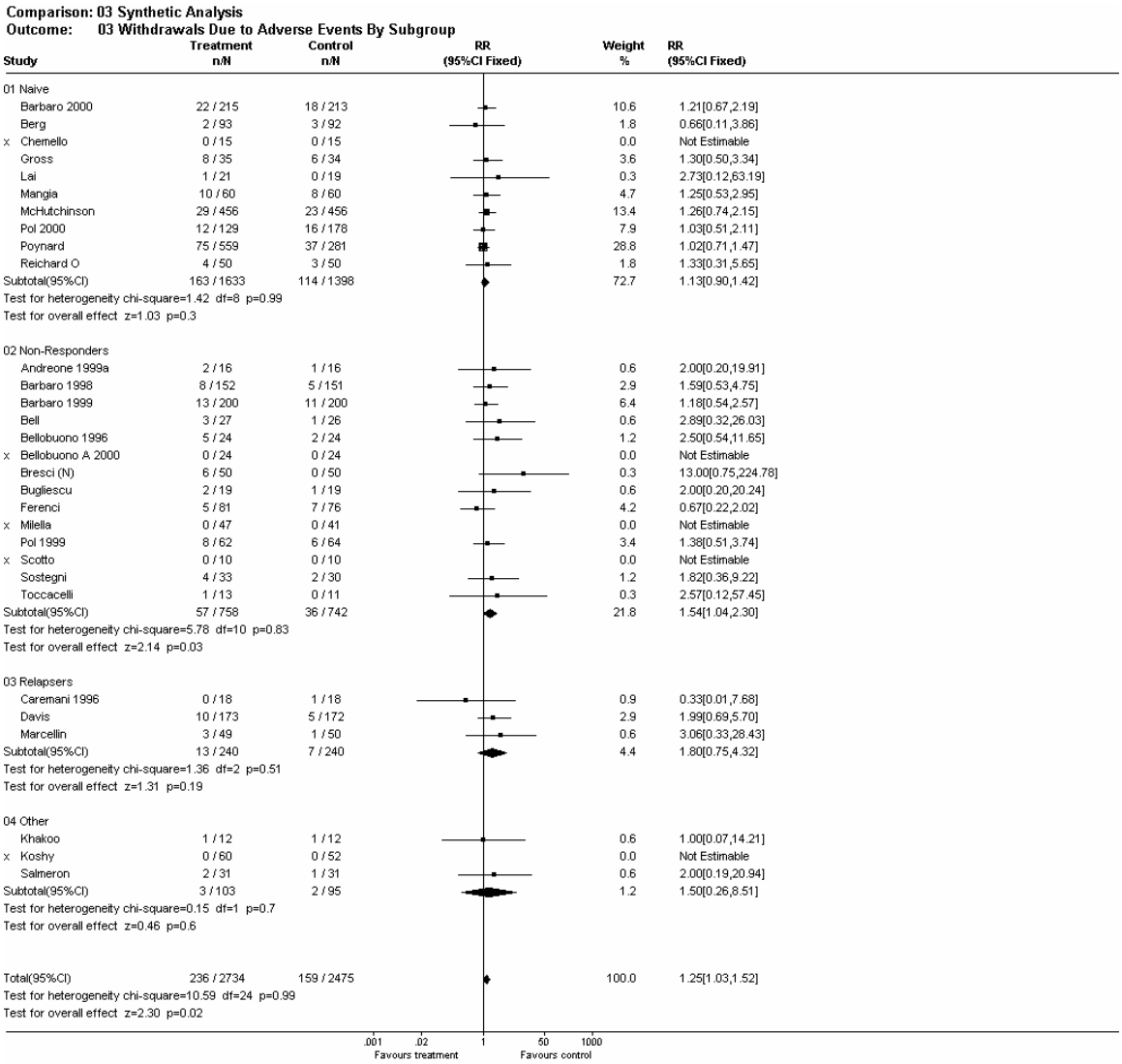
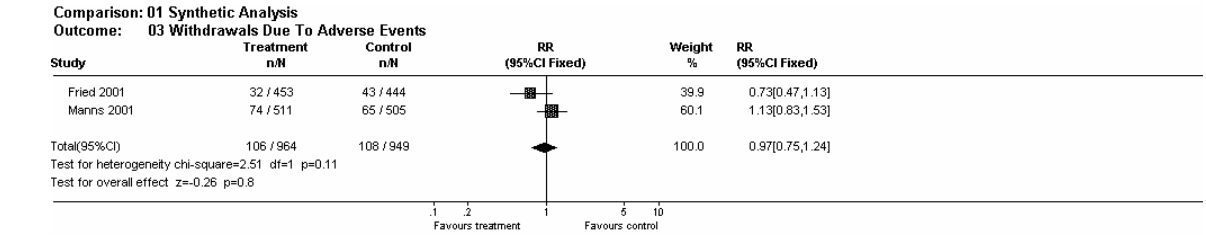


Figure 3b: Withdrawals due to adverse events,
pegylated IFN plus ribavirin versus IFN plus ribavirin



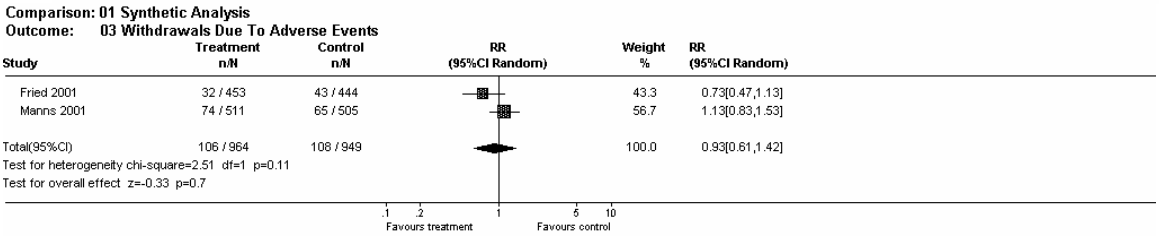


Figure 4a: Risk of not having sustained viral responses, IFN plus ribavirin versus IFN

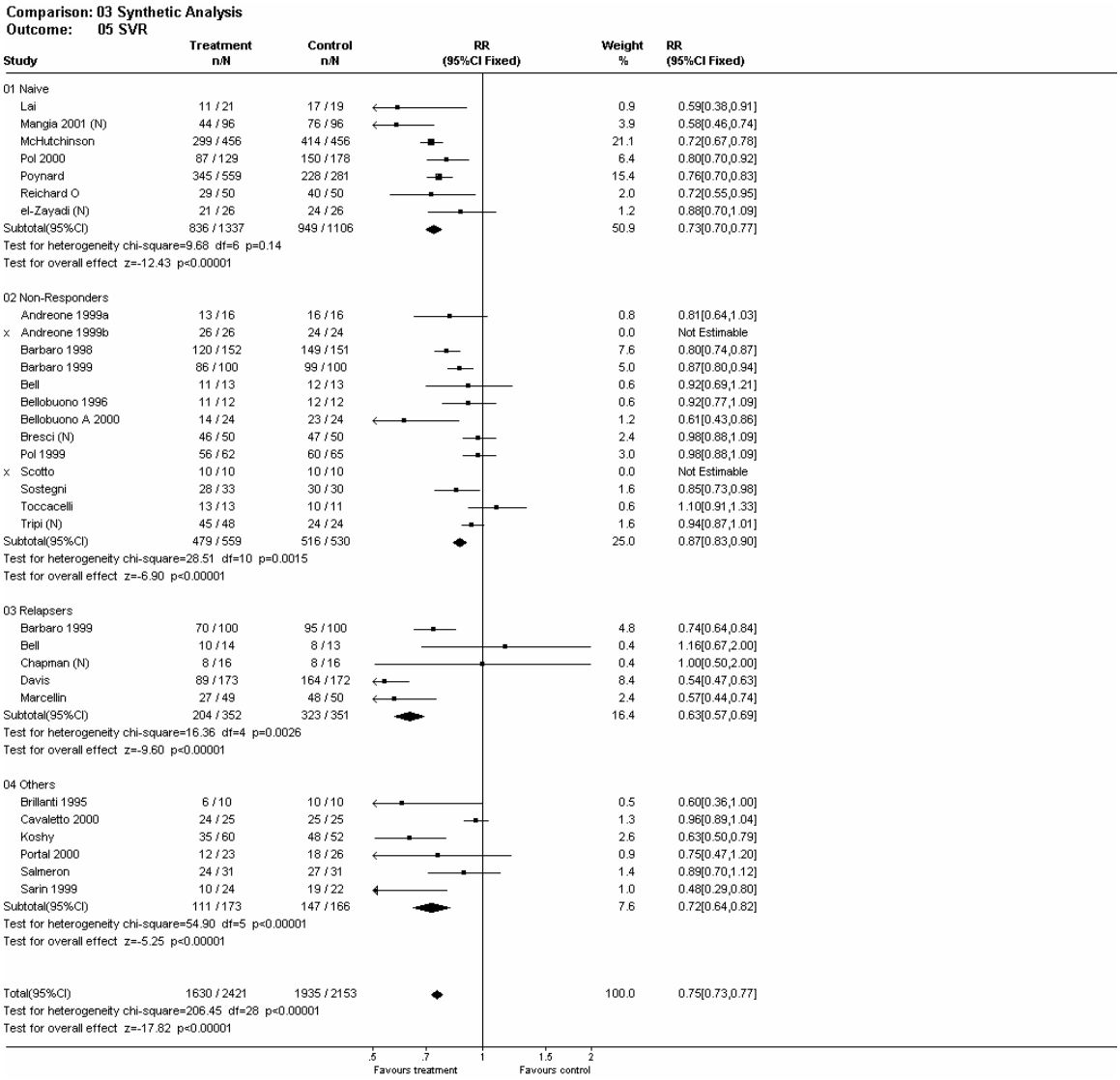


Figure 4b: Risk of not having sustained viral responses, pegylated IFN plus ribavirin versus IFN plus ribavirin