A decade of trials of interferon-alpha for chronic hepatitis C: a meta-regression analysis

Tine F, Attanasio M, Russo F, Pagliaro L

CRD summary

This review examined differences between trials assessing the effectiveness of interferon-alpha (IFN) for naive patients with chronic hepatitis C. The authors concluded that differences were mainly associated with different IFN regimens, but hepatitis C virus genotypes, study quality and reporting could also help explain them. The conclusions may not be very reliable as studies might have been missed and error and bias cannot be ruled out.

Authors' objectives

To assess differences in the characteristics of trials that have examined the effectiveness of interferon-alpha (IFN) for the treatment of naive patients with chronic hepatitis C.

Searching

MEDLINE was searched from 1989 to the end of 2000; the search terms were reported. In addition, bibliographies, citations and references from published meta-analyses were screened. The studies were limited to those published in English.

Study selection

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) were eligible for inclusion. Studies that were clinical series were excluded. The duration of follow-up after completion of IFN treatment ranged from 3 to 40 months.

Specific interventions included in the review

Studies that assessed the effectiveness of IFN as either a monotherapy or combined therapy regimen, with placebo, no treatment or a different regimen representing standard treatment, were eligible for inclusion. The specific interventions assessed in the review were: standard IFN regimens versus placebo or no treatment; different IFN regimens versus standard IFN regimens; and standard IFN regimens versus IFN in combination with either ribavirin, ursodeoxycholic acid, non-steroidal anti-inflammatory drugs (tenoxicam or ketoprofen), iron depletion therapy, corticosteroids, N-acetyl cysteine, thymosin alpha, polyunsaturated phosphatidyl-choline, granulocyte macrophage colony stimulating factor, amantadine, or antioxidant therapy.

Participants included in the review

Studies that included patients with chronic hepatitis C and amino-transferase elevation that had never been treated were eligible for inclusion. Studies that included patients with acute hepatitis, normal serum alanine aminotransferases (ALT), nonresponders or relapsers after interferon, coinfections (hepatitis B virus, human immunodeficiency virus), orthotopic liver transplant carriers, common hepatitis C virus (HCV)-associated diseases, or haemodialysed patients were excluded. In the included studies, the mean age of the participants ranged from 44 to 49 years and the proportion of males from 61 to 67%.

Outcomes assessed in the review

No inclusion criteria were stated in relation to the outcomes. Studies that did not report data on the usual outcomes were excluded, although outcomes classed as unusual were not defined. The primary outcome assessed was normal ALT after at least 6 months after treatment completion. Sustained virological (RNA-SR) response was also evaluated as a comparison.

How were decisions on the relevance of primary studies made?

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality

Study quality was assessed according to the Jadad quality criteria: methods of randomisation, blinding, and the reporting of drop-outs and withdrawals. Concealment of allocation and whether a sample size calculation had been performed were also assessed. The authors did not report how many reviewers performed the quality assessment, or how any disagreements were resolved.

Data extraction

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The odds ratio (OR) for normal ALT after at least 6 months after treatment completion was calculated for each trial.

Methods of synthesis

How were the studies combined?

The studies were combined using a random-effects meta-analysis. Publication bias was not assessed.

How were differences between studies investigated?

Differences between the studies were assessed using the Q statistical test. In addition, further pre-planned meta-regression analyses and sub-group analyses were undertaken.

Results of the review

One hundred and eighteen RCTs (n=15,060) were included in the review.

Nineteen per cent of the trials scored at least 3 on the Jadad quality score. Twenty-five per cent of the trials reported some form of blinding, with 14 of the 30 trials reporting a statement on double-blinding; however, only 4 trials actually described the method of blinding. A sample size calculation was reported in 20% of the trials, and allocation concealment was considered adequate in only 12% of the trials.

The pooled OR for treatment effect varied according to the interventions assessed. There was a statistically significant increase in sustained ALT normalisation with IFN treatment in comparison with placebo or no treatment (32 RCTs, n=2,499); the OR was 9.5 (95% confidence interval, CI: 6.3, 14.2). No significant heterogeneity was observed across this group of trials.

There was a statistically significant effect of treatment with standard IFN compared with alternative IFN schedules (43 RCTs, n=7,454); the OR was 1.6 (95% CI: 1.4, 1.9). Significant heterogeneity was observed across these trials.

There was a statistically significant effect of treatment with IFN in combination with another drug versus IFN alone (30 RCTs, n=4,737); the OR was 2.0 (95% CI: 1.6, 2.6). However, these trials were significantly heterogeneous.

The meta-regression (complete data set, 171 trial arms; n=10,580) showed that sustained response was most likely in experimental arms of IFN in combination with ribavirin or other drugs (OR=2.4); in arms using a yearly dosing schedule (OR=2.0); in studies in which the principal trial author was from Asia, (OR=1.7); in trials with a sample size greater than 200 participants (OR=1.4); and in trial arms enrolling less than 50% of cirrhotics (OR=1.3). The results of the meta-regression also showed a number of significant interaction effects. The effect of trial quality interacted with the recorded funding body, with more benefit observed if the body was not for profit and less if it was for profit. The effect of trial funding also interacted significantly with the location of the first author, with more benefit being observed if the first author was from Asia. Overall, the three main effects of experimental arm, cirrhosis, funding, and the interaction effect of type of funding and the location of the principal author, explained 31% of the between-study variability.

The results of the meta-regression on the sub-group of trials reporting data on HCV genotype (93 arms; n approximately 7,000) showed that enrolling less than 50% of patients with genotype 1 or 4 per arm, and publishing the results of the study in a specialist journal, were significant predictors of either biochemical (transaminases) or virological (HCV-RNA) sustained response in a model including the same main effects identified in the complete data set analysis

(reported above).

Authors' conclusions

Heterogeneity was mainly associated with different IFN regimens along time, HCV genotype, and variables of quality and reporting.

CRD commentary

The review question was reasonably broad, but had been defined in terms of the interventions, participants and study designs. The literature search was limited to only one database and the checking of references. No efforts were made to locate unpublished studies or to include studies not published in English. This meant that some relevant studies might have been missed, and both publication and language bias may have been introduced into the review. The authors did not investigate the possibility of publication bias. The methods of selecting the studies for inclusion and extracting the data were not reported, thus it is impossible to know whether any steps were taken to minimise reviewer bias and errors in the review process. Study quality was assessed, but the procedure for undertaking the assessment was also not reported.

No details on the primary studies were presented. Therefore, it is not possible to tell whether the authors' conclusions are consistent with the evidence reviewed. A number of trials were initially identified then excluded from the analysis; no further details of these trials were reported. The use of a meta-analysis to combine the studies appears to have been appropriate, and the authors adequately explored further differences between the studies using meta-regression techniques. Since some relevant studies might have been missed, and reviewer error or bias cannot be ruled out, the authors' conclusions may not be very reliable.

Implications of the review for practice and research

The authors did not state any implications for practice or further research.

Bibliographic details

Tine F, Attanasio M, Russo F, Pagliaro L. A decade of trials of interferon-alpha for chronic hepatitis C: a meta-regression analysis. Contemporary Clinical Trials 2005; 26(2): 179-210

PubMedID

15837440

DOI

10.1016/j.cct.2004.12.009

Indexing Status

Subject indexing assigned by NLM

MeSH

Hepatitis C, Chronic /drug therapy; Humans; Interferon-alpha /therapeutic use; Logistic Models; Randomized Controlled Trials as Topic /statistics & numerical data; Time Factors; Treatment Outcome

AccessionNumber

12005008281

Date bibliographic record published

31/01/2006

Date abstract record published

31/01/2006

Record Status

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.