A prospective, randomized trial comparing lymphoblastoid to recombinant interferon alfa 2a as therapy for chronic hepatitis C


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of lymphoblastoid interferon (IFN-N1) and recombinant interferon alfa 2a (IFN-alpha2a) were compared, both are forms of interferon. Both interferons were administered in the same way. Intra-muscular injections of IFN-alpha2a or IFN-alphaN1 were given in doses of 6 Million units (MU) thrice weekly until both alanine transaminase (ALT) and aspartate transaminase (AST) normalised and remained normal for at least 4 weeks. All these patients were then given doses of 3 MU 3 times a week for a total of 12 months of treatment. The higher dose was again given if any patient's levels of ALT/AST went above the upper limit of normal. Treatment was discontinued in patients who did not respond in 24 weeks of therapy.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients with chronic hepatitis caused by hepatitis C virus (HVC).

Setting
It was not explicitly stated, but the setting appears to be an outpatient clinic. The study was conducted at the Center of Liver Diseases at Policlinic Hospital, University of Milan, Italy.

Dates to which data relate
Patients were enrolled into the clinical trial from January 1991 to November 1992. Clinical data were collected until November 1994. No related information is given on cost data. The price year was not stated.

Source of effectiveness data
Evidence for final outcomes was derived from a single study.

Link between effectiveness and cost data
No details were given of the methods of estimating cost data, nor of any links between effectiveness and cost data.

Study sample
The sample size needed to detect a 20% difference in the biochemical response between treatments was 129 in each group, assuming that 40% of the patients would show normal ALT/AST values during the first 6 months. A total of 258
patients were recruited, 129 in each group. Diagnosis was established on the basis of liver biopsy findings, serum HCV antibodies and abnormal serum transaminase levels. The number invited to participate who refused was not mentioned. Criteria for inclusion were; no previous treatment, high serum ALT and AST values for at least 1 year previously, serum anti-HCV by EIA-2, and histological features of chronic hepatitis. Patients with drug or alcohol induced liver diseases were excluded. Other exclusion criteria were pregnancy, jaundice, ascites, encephalopathy, upper gastrointestinal haemorrhage, thrombocytopenia or leucopenia. Numbers excluded from the trial for any reason were not given.

**Study design**
This was a randomised controlled trial at a single centre. Both cohorts were treated for 12 months and then monitored for a further 12 months. Patients were stratified into 3 groups according to severity of disease and then randomly allocated to treatment or control groups. The loss to follow up was 9.3% (24 patients); 8.5% (11 patients) in the IFN-alpha2a group and 10% (13 patients) in the IFN-alphaN1 group. Nine of the 24 dropped out because of side effects in the first 8 months, (3% and 4%, respectively, for the IFN-alpha2a and IFN-alphaN1 groups). At month 24 only 130 patients agreed to have a liver biopsy. Liver biopsies were performed by a blinded independent observer. Blinding at other stages of the study was not mentioned.

**Analysis of effectiveness**
The analysis was based on treatment completers only. Primary health outcomes were normal transaminases (ALT and AST values) and undetectable HCV RNA by reverse-transcription polymerase chain reaction (RT-PCR) after 12 months treatment and at 24 months (12 months after treatment was discontinued). Adverse reactions were also recorded. Most patients (88% in the IFN-alpha2a group and 93% in the IFN-alphaN1 group) suffered flu-like symptoms. Other adverse reactions were: myalgias, headache, arthralgias, loss of libido, hypothyroidism, psychological depression, thrombocytopenia, hair loss, lichen ruben planus, hyperthyroidism and angina. The groups were shown to be comparable in terms of epidemiological, virological and clinical features.

**Effectiveness results**
In the IFN-alpha2a group 31 (26%) had normal ALT and AST levels and negative HVC RNA at 12 months and 19 (16%) at 24 months. In the IFN-alphaN1 group 28 (24%) had normal ALT and AST levels and negative HVC RNA at 12 months and 20 (17%) at 24 months. Differences between groups were not significant. The overall prevalence of drug-related side effects excluding flu-like syndrome was 23% in the IFN-alpha2a group and 37% in the IFN-alphaN1 group (P = 0.025).

**Clinical conclusions**
The outcome of treatment in chronic hepatitis C patients was not improved by the administration of high cumulative doses of lymphoblastoid IFN (IFN-alphaN1) compared with recombinant interferon (IFN-alphaN1).

**Measure of benefits used in the economic analysis**
The measure of benefits were the number of cases with drug-related side-effects avoided (excluding flu-like syndrome).

**Direct costs**
Although the total dose quantities were analysed separately from the costs, no details were given of how the cost data were collected. Overall costs for treating 118 patients (treatment completers) with IFN-alpha2a and 116 treatment completers with IFN-alphaN1 and the cost for each sustained complete response (a patient with normal ALT and AST and negative HCV RNA at 24 months) were provided. The price year was not stated.

**Currency**
Italian lira (L) and US dollars ($).

**Sensitivity analysis**
None were carried out.

**Estimated benefits used in the economic analysis**
The overall prevalence of drug-related side effects excluding flu-like syndrome was 23% in the IFN-alpha2a group and 37% in the IFN-alphaN1 group.

**Cost results**
Overall costs for treating 118 patients with IFN-alpha2a were 955 million lira and for treating 116 patients with IFN-alphaN1 were 1 billion lira.

**Synthesis of costs and benefits**
Costs and benefits were not combined since the intervention was both more expensive and had a higher rate of side effects than the comparator.

**Authors’ conclusions**
The outcome of treatment in chronic hepatitis C patients was not improved by the administration of high cumulative doses of lymphoblastoid IFN. Treatment with both kinds of IFN produced poor responses at high cost.

**CRD COMMENTARY - Selection of comparators**
The authors have given a justification for their choice of comparator, however some discussion of alternative treatments, if any, and the inclusion of the "do-nothing" option would have been a useful and relevant option to consider.

**Validity of estimate of measure of benefit**
The estimate of the measure of benefit was questionable due to potential biases accruing from the principle (treatment completers only) used in the analysis, and the fact that the projected statistical power of tests could not be reached.

**Validity of estimate of costs**
So little information was given about cost collection or analysis that the results were questionable. The price year was not provided.

**Other issues**
The authors’ conclusions were justified, however the issue of generalisability cannot be assessed due to the lack of detail in the costing.

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