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Interferon beta for chronic hepatitis B (Protocol)

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[Intervention Protocol]

Interferon beta for chronic hepatitis B

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the beneficial and harmful effects of interferon beta for patients with chronic hepatitis B.

BACKGROUND

Description of the condition

Hepatitis B is a disease of the liver caused by the hepatitis B virus (HBV), which has a partially double-stranded circular DNA (Carman 1992). HBV infection causes a significant worldwide health problem. Approximately one third of the world population has serological evidence of past or present infection by HBV (EASL 2009). An estimated 350 million are chronically infected with HBV (Lavanchy 2004), and 600,000 persons die each year because of acute or chronic hepatitis B (WHO 2008). About 25% of the chronically infected adults die from either liver cirrhosis or cancer caused by the chronic infection. The virus is transmitted through contact with the blood or other body fluids of an infected person. The HBV is 50 to 100 times more infectious than human immunodeficiency virus (WHO 2008). The diagnosis of chronic HBV infection is based on persistence of HBsAg in plasma for more than six months; plasma IgG anti-HBc is positive, while plasma IgM anti-HBc is negative (Chapman 2008b).

Sexual transmission (Alter 1986; Kingsley 1990), vertical transmission (Beasley 1977), and unsafe injections (Kane 1999), including intravenous drug addiction (Broers 1998), are important routes of infection with HBV. Household contact (Vegnente 1992) and occupational exposure, such as that of health-care professionals (Lauer 1979; Hu 1991; Fernandes 1999), blood products (Colombo 1987; Saxena 1999), and haemodialysis (Williams 1974; Mioli 1992) are other risk factors.

Chronic hepatitis B may present as HBeAg-positive or HBeAg-negative hepatitis B. HBeAg-positive chronic hepatitis B is due to wild-type HBV; it represents the early phase of chronic HBV infection. HBeAg-negative chronic hepatitis B is due to a naturally occurring HBV variant with mutation in the pre-core or the basic core promoter regions of the genome or both; it represents the late phase of chronic HBV infection (EASL 2009). When given interferon alpha, the response is lower in HBeAg-negative chronic hepatitis even when patients are given longer courses of treatment (Chapman 2008a).

Morbidity and mortality in patients with chronic hepatitis B are linked to development of cirrhosis or hepatocellular carcinoma. The five-year cumulative risk of developing cirrhosis ranges from

8% to 20% (Marcellin 2005). Although the incidence of hepatocellular carcinoma varies geographically, it has increased worldwide; about 75% of the patients with hepatocellular carcinomas have HBV infection (Marcellin 2009). After 10 years of chronic hepatitis B infection, about 20% of patients have progressed to cirrhosis and about 5% have progressed to hepatocellular carcinoma (Ikeda 1998).

Description of the intervention

Interferon beta is a naturally occurring substance, which is obtained from cultured human fibroblasts (Chopra 2007). It differs from the naturally occurring human protein by a single amino acid substitution and the lack of carbohydrate side chains (Jacobs 2000; Panitch 2002). It is very similar in structure to interferon alpha. In vitro, interferon beta has been shown to inhibit the replication of various viruses and to stimulate the immune system (Chopra 2007). Interferon beta modify biological responses through cell surface receptor interactions (Jacobs 2000; Panitch 2002). Immunomodulatory effects attributed to interferon beta include enhancement of suppressor T cell activity, reduction of pro-inflammatory cytokines, down-regulation of antigen presentation, and reduced trafficking of lymphocytes (Sheremata 1995; Goodin 2002).

How the intervention might work

Interferon alpha is an immunomodulator and plays a role in the treatment of chronic hepatitis B (Scully 1990). Interferon beta is also an immunomodulator, so it could play a similar role in the treatment of chronic hepatitis B.

Interferon beta has been demonstrated to have anti-viral and immunomodulatory properties against HBV (Guan 1996). Reduction of both HBV-DNA and aminotransferase levels in the serum have been observed with the use of interferon beta for chronic hepatitis B (Arase 1996; Guan 1996). It is necessary to administer interferon beta intravenously because it is promptly inactivated. However, with the substitution of the cysteine amino acid by serine at position 17 of the molecule, interferon beta becomes more stable, and subcutaneous administration becomes possible (Eisenberg 1986; Guan 1996). Treatment with interferon beta has been well tolerated. However, fever, granulocytopaenia (Eisenberg 1986; Kagawa 1993; Arase 1996), and proteinuria (Eisenberg 1986) have been observed in patients exposed to interferon beta.

Why it is important to do this review

Currently, several drugs are available for the treatment of chronic hepatitis B which are lamivudine, adefovir, entecavir, telbivudine, tenofovir, interferon alpha, and pegylated interferon alpha (Lok 2007; EASL 2009).

The available interventions do only work in some patients, cause adverse events, and are expensive (Lok 2007; EASL 2009) which gives the reason for alternative interventions to be sought. Interferon beta could present such an alternative. As we did not identify any meta-analyses or systematic reviews evaluating the beneficial and harmful effects of interferon beta for patients with chronic hepatitis B, we took upon this Cochrane Hepato-Biliary Group systematic review.

OBJECTIVES

To evaluate the beneficial and harmful effects of interferon beta for patients with chronic hepatitis B.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised clinical trials assessing the beneficial and harmful effects of interferon beta for chronic hepatitis B, irrespective of publication status, language, or blinding. Quasi-randomised and observational studies that will be obtained with the searches will be considered only for the report of harms.

Types of participants

- Children and adults of either sex having chronic HBV infection with or without cirrhosis, without limitations to mode of acquisition, or region of residence.
- Patients irrespective of whether they are HBeAg-positive or HBeAg-negative, treatment-naive, non-responders, or relapsers to previous antiviral treatments.
- Patients with or without concomitant human immunodeficiency virus (HIV) infection, hepatitis C virus, or hepatocellular carcinoma.
- Patients with or without liver transplantation or renal failure.

Types of interventions

- Interferon beta at any dosage versus placebo or no intervention.
- Interferon beta at any dosage versus interferon alpha, or any other anti-viral drug, excluding patients treated with vaccine.

Co-interventions will be allowed if administered equally to all groups in a trial.

Types of outcome measures

HBeAg-positive patients

Primary outcomes

1. All-cause mortality.
2. Proportion of patients with decompensation of liver disease.
3. Proportion of patients without disappearance of serum HBV DNA (> 10^5 copies/mL) at the end of treatment or at six-month post-treatment follow-up.

Secondary outcomes

4. Proportion of patients without HBeAg seroconversion from HBeAg-positive status to anti-HBe positive status at the end of treatment or at six-month post-treatment follow-up.
5. Proportion of patients without disappearance of HBsAg at maximum follow-up after end of treatment.
6. Proportion of patients without decrease in HBV DNA levels to less than 100,000 copies/mL or 2000 IU/mL at the end of treatment and at six month post-treatment follow-up.
7. Proportion of patients without histological improvement.
8. Proportion of patients without normalisation of liver enzyme at the end of treatment and at six-months post-treatment follow-up.
9. Proportion of patients with serious adverse events and proportion of patients with non-serious adverse events. Serious adverse events are defined according to the International Conference on Harmonisation (ICH) Guidelines (ICH-GCP 1997) as any event that leads to death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, and any important medical event, which may have jeopardised the patient or requires intervention to prevent it. All other adverse events will be considered non-serious.
10. Proportion of patients discontinuing treatment.
11. Quality of life.

HBeAg-negative patients

Primary outcomes

1. All-cause mortality.
2. Proportion with decompensation of liver disease.
3. Proportion without disappearance of serum HBV DNA (> 10^4 copies/mL) at the end of treatment or at six-month post-treatment follow-up.

Secondary outcomes

4. Proportion without disappearance of post-treatment HBsAg at maximum follow-up after the end of treatment.
5. Proportion without histological improvement.
6. Proportion without return of liver enzyme levels to normal range at the end of treatment and six-month post-treatment sustained biochemical response.
7. Proportion with serious adverse events and proportion with non-serious adverse events. Serious adverse events are defined according to the International Conference on Harmonisation (ICH) Guidelines (ICH-GCP 1997) as any event that leads to death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, and any important medical event, which may have jeopardised the patient or requires intervention to prevent it. All other adverse events will be considered non-serious.
8. Proportion of patients discontinuing treatment.
9. Quality of life.

Search methods for identification of studies

Electronic searches

We will search *The Cochrane Hepato-Biliary Group Controlled Trials Register* (Gluud 2010), the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library*, *MEDLINE*, *EMBASE*, and *Science Citation Index Expanded* (Royle 2003). We have given the preliminary search strategies in Appendix 1 with the time span for the searches. The search strategies may be improved at the review stage development.

Searching other resources

The bibliographic references of identified randomised clinical trials, textbooks, review articles, and meta-analyses will be checked in order to find randomised clinical trials, not identified by the electronic searches. The principal authors of the identified randomised clinical trials will be approached and inquired about additional randomised clinical trials they might know of. Pharmaceutical companies involved in the production of interferon beta will be contacted in order to obtain unpublished randomised clinical trials.

Data collection and analysis

We will perform the review and meta-analyses following the recommendations of The Cochrane Collaboration (Higgins 2009) and *The Cochrane Hepato-Biliary Group Module* (Gluud 2010). The analyses will be performed using Review Manager 5 (RevMan 2008).

Selection of studies

We will list the identified trials; two of the authors, YS and MQ, will independently assess their fulfilment of the inclusion criteria. We will list the excluded trials with the reason for exclusion. Disagreements will be resolved by discussion between the two authors, YS and MQ. If not, NI will be the arbitrator.

Data extraction and management

We will use a template form for data collection and extraction of data on methods, participants, interventions, and outcomes. If more than one publication on each randomised clinical trial is identified, data will be extracted from the publication, providing the most pertinent information. Two of the authors, MS and MEA, will extract data independently of one another. Disagreements will be resolved by discussion between MS and MEA. If not, NI will be the arbitrator.

Assessment of risk of bias in included studies

The methodological quality is defined as the confidence that the design and report of a published trial will restrict bias in the intervention comparison (Moher 1998). According to empirical evidence (Schulz 1995; Jadad 1996; Moher 1998; Jüni 2001; Kjaergard 2001; Wood 2008), the evaluation of the risk of bias could be achieved through assessing the following domains:

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards and throwing dice are adequate if performed by an independent adjudicator.
- Uncertain risk of bias: the trial is described as randomised, but the method of sequence generation was not specified.
- High risk of bias: the sequence generation method is not, or may not be, random. Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate patients are inadequate and will be excluded for the assessment of benefits but not for harms.

Allocation concealment

- Low risk of bias: allocation was controlled by a central and independent randomisation unit, sequentially numbered, opaque and sealed envelopes or similar, so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
- Uncertain risk of bias: the trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. Quasi-randomised studies will be excluded for the assessment of benefits but not for harms.

Blinding

- Low risk of bias: the trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
- Uncertain risk of bias: the trial was described as blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trial.
- High risk of bias, the trial was not blinded, so that the allocation was known during the trial.

Incomplete outcome data

- Low risk of bias: the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Uncertain risk of bias: the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- High risk of bias: the number or reasons for dropouts and withdrawals were not described.

Selective outcome reporting

- Low risk of bias: pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
- Uncertain risk of bias: not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Baseline imbalance

- Low risk of bias: if there was baseline balance in important characteristics.
- Uncertain risk of bias: if the baseline characteristics were not reported.
- High risk of bias: if there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation.

Early stopping

- Low risk of bias: if the sample size calculation was reported and the trial was not stopped, or the trial was stopped early by formal stopping rules at a point where the likelihood of observing an extreme intervention effect due to chance was low.
- Uncertain risk of bias: if sample size calculation was not reported and it is not clear whether the trial was stopped early or not.
- High risk of bias: if the trial was stopped early due to informal stopping rules or the trial was stopped early by a formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was high.

Vested interest bias

- Low risk of bias: if there was no risk of vested interests on the side of researchers, manufacturers, or funding bodies; or any personal conflicts by the authors of the trial publication that might have

unduly influenced judgements were disclosed in an honest and upright manner.
- Uncertain risk of bias: if it is not possible to say that there were or there were not any financial interests on the side of researchers, manufacturers, or funding bodies reported in the trial publications.
- High risk of bias: if there was risk for vested interests, eg, the trial was funded by a drug manufacturer, or researches had received money for the performance of the trial, and interests like these could have influenced the results of the trial report.
'Trials with low risk of bias' shall be considered those trials that are assessed as trials having 'low risk of bias' in all of the specified individual domains. Trials with 'uncertain risk of bias' or 'high risk of bias' shall be considered those trials that are assessed as trials having 'uncertain risk of bias' or 'high risk of bias' in one or more of the specified individual domains.

Measures of treatment effect

Dichotomous data
The relative risks with 95% confidence intervals (CI) will be calculated by both the fixed-effect (DeMets 1987) and random-effects models (DerSimonian 1986).
Continuous data
Mean differences with 95% CI will be calculated by both the fixed-effect model and random-effects model.
In case when the overall results are statistically significant by the fixed- and random-effects models, relative risk reduction (RRR), and, if relevant, the number-needed-to-treat (NNT) and the number-needed-to-harm (NNH) will be calculated.

Unit of analysis issues

In case no randomised clinical trials are identified, we will summarise the results of the prospective cohort studies, that we might obtain with the search, in the 'discussion' section.The summary will be conceived with the purpose of guiding the researchers who wish to conduct randomised clinical trials on the effect of interferon beta for chronic hepatitis B.

Dealing with missing data

All analyses will be performed according to the intention-to-treat method, using the last reported observed response ('carry forward'), and including all participants irrespective of compliance or follow-up. In addition, 'a worst case scenario' analysis will be performed, and participants with missing data will be considered as treatment failures.

Assessment of heterogeneity

Statistical heterogeneity will be assessed both by inspection of graphical presentations ('funnel plot') (Egger 1997) and calculating the Chi^2 test. The statistical heterogeneity is defined significant, if $P < 0.1$.

Assessment of reporting biases

Funnel plot asymmetry will also be used to assess bias if we have a minimum number of ten trials (Egger 1997).

Data synthesis

Due to the underlying assumptive differences, results from the fixed-effect model and the random-effects model may differ to a non-ignorable extent. In case such discrepancies are observed, the results will be interpreted according to the implications of the subgroup and heterogeneity analyses, and according to confidence intervals of the two models.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analysis with:
- Age of patients; children compared to adults.
- HBeAg-positive and HBeAg-negative chronic hepatitis B.
- Patients with cirrhosis compared to patients without cirrhosis.
- Treatment naive compared to relapses or non-responders.
- Total dosage of interferon beta; low dose compared to intermediate dose compared to high dose.
- Genotypes of HBV. Co-infection with HIV or hepatitis C virus at entry, compared to without co-infection.
- Trials with low risk of bias compared to trials with unclear or high risk of bias.
- Trials without losses to follow-up compared to trials with losses to follow-up.
- Follow-up at the end of treatment compared to follow-up at six months or more than six months after treatment.
- Trials published as full paper articles compared to trials published as abstracts only.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Database	Time span of search	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at the review stage.	((interferon* AND beta*) OR beta*eron OR avonex OR rebif OR cinnovex OR extavia) AND (chronic AND ('hepatitis B' OR HBV))
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Latest issue.	#1 MeSH descriptor Interferon-beta explode all trees #2 ((interferon* AND beta*) OR beta*eron OR avonex OR rebif OR cinnovex OR extavia) #3 (#1 OR #2) #4 MeSH descriptor Hepatitis B, Chronic explode all trees #5 (chronic AND ('hepatitis B' OR HBV)) #6 (#4 OR #5) #7 (#3 AND #6)
MEDLINE(Ovid SP)	1950 to the date of search.	1. exp Interferon-beta/ 2. ((interferon$ and beta$) or beta?eron or avonex or rebif or cinnovex or extavia).mp. [mp=title, original title, abstract, name of substance word, subject heading word] 3. 1 or 2 4. exp Hepatitis B, Chronic/ 5. (chronic and ('hepatitis B' or HBV)).mp. [mp=title, original title, abstract, name of sub-

(*Continued*)

		stance word, subject heading word] 6. 4 or 5
EMBASE (Ovid SP)	1980 to the date of search.	1. exp Beta Interferon/ 2. ((interferon$ and beta$) or beta?eron or avonex or rebif or cinnovex or extavia).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 3. 1 or 2 4. exp Hepatitis B/ 5. (chronic and ('hepatitis B' or HBV)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 6. 4 or 5 7. 6 and 3 8. (random$ or blind$ or placebo$ or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 9. 8 and 7
Science Citation Index Expanded (http://apps.isiknowledge.com)	1900 to the date of search.	# 1 TS=((interferon* AND beta*) OR beta*eron OR avonex OR rebif OR cinnovex OR extavia) # 2 TS=(chronic AND ('hepatitis B' OR HBV)) # 3 #2 AND #1 # 4 TS=(random* OR blind* OR placebo* OR meta-analysis) # 5 #4 AND #3

WHAT'S NEW

Last assessed as up-to-date: 28 February 2010.

Date	Event	Description
23 April 2010	Amended	Minor amendment in the authors tasks at the review stage.

CONTRIBUTIONS OF AUTHORS

NI, MEA, MQ, MS, and YS have contributed to a draft version of the protocol, and NI commented on and approved of the version submitted for peer reviewing.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Cochrane Hepato-Biliary Group, Denmark.

External sources

- No sources of support supplied

NOTES

This is an updated and completely changed version of a previous Cochrane Hepato-Biliary Group protocol by Saconato H, Atallah ÁN, Souza GM, and Parise ER, published in The Cochrane Library in 2002 (Saconato 2002). That protocol was never turned into a Cochrane review.