# INTERFERON ALPHA FOR HBeAg POSITIVE CHRONIC HEPATITIS B: SYSTEMATIC REVIEW

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BACKGROUND

Hepatitis B virus (HBV) infection, together with hepatitis C and alcohol abuse, is among the leading causes of cirrhosis and hepatocellular carcinoma (HCC) worldwide (1,2). It thus represents a relevant cause of morbidity and mortality (3-5), and induces substantial direct and indirect social costs. Effective treatment of HBV-related conditions would significantly reduce the global burden of chronic liver disease.

α interferon has been the mainstay of therapy for chronic hepatitis B since the early 80's. Meta-analyses (6-9) of randomized clinical trials (RCTs) conclusively prove its effectiveness in normalizing alanine aminotransferases (ALT) and clearing HBeAg and HBV-DNA from blood in 25-40% of patients treated. No definite data are available from these reviews on improvements of liver histology. Standardized response criteria have been set by the use of these "surrogate" markers of cure (10, 11), on the ground of clinical and biological plausibility. "True" disease endpoints (i.e. progression to cirrhosis, to hepatocellular carcinoma and death) cannot usually be assessed in short-term trials of IFN due to the slow natural course of chronic hepatitis B. A major issue of concern is the fact that RCTs of IFN for chronic hepatitis B have been mostly performed in patients without advanced fibrosis or cirrhosis. The transferability of results to the whole spectrum of subjects with chronic liver disease due to HBV is hence questionable.

Since IFN is today in widespread use, in alternative to lamivudine, as the first-line therapy for chronic hepatitis B (1, 2, 10, 11), no additional prospective cohort studies on the course of untreated disease will be feasible. Long-term retrospective or prospective studies to evaluate the benefits of IFN therapy on true endpoints, i.e. prevention of cirrhosis, liver failure, HCC and death, will also difficult to perform due to the prolonged and slow course of the disease.

The aim of this meta-analysis is to review and update the available evidence in order to estimate the effectiveness of alfa-IFN in chronic on "surrogate markers" of response and its long-term benefit.

**MATERIALS AND METHODS**

The meta-analysis was performed according to the criteria set by Lau et al. (12). The primary source of studies reviewed was the MEDLINE data-base (1985-2002) (key words: chronic hepatitis, hepatitis B, interferon alpha, RCT, randomized, clinical trial, long-term study). Reference lists of all available review articles and primary studies were also checked in order to identify other studies not found by computer search. Potentially relevant papers were initially classified into two subsets (1: RCTs; 2: cohort studies).

Studies allocated to subset 1 were included in the meta-analysis if they were truly randomized and had a crossover or a parallel design comparing different schedules of treatment to a control group receiving no treatment; if they had been published in English as full length papers; if they included adult patient (older than 18 years) with biopsy-proven chronic hepatitis B with or without cirrhosis, and with abnormal aminotransferases levels for at least 3 months, without evidence of HDV superinfection and HIV co-infection or of HCV coinfection (since 1990 beyond); if they had used α interferon (recombinant α2a or α2b, human lymphoblastoid αN1 or human leucocyte derived αN3) in naïve patients. Studies were excluded if they used IFN in combination with other antiviral or immunomodulatory agents (except steroid induction); if they

had not been published in English or as a preliminary report subsequently published as final paper; if they randomized only primary responders, or pooled randomized with nonrandomized patients. Duplicate reports, as well as studies reported solely in abstracts, letters and preliminary reports were also excluded. Abstracts were excluded because of the potential risk for duplication of the results and a substantial and uninterpretable bias could be introduced. 24 RCTs (13-35) from subset 1 were included in the meta-analysis (Table 1). Main sociodemographic features of patients and the schedules of treatment were analysed in order to verify their actual comparability. Abstraction of data was independently performed by two readers (D. D. B. and C.C.), who compared results and then achieved consensus.

The evaluation of therapeutic efficacy was performed by an "intention to treat" strategy. Treatment effectiveness was assessed on "surrogate markers" of response such as stable normalization of ALT, sustained loss of HBV-DNA, clearance of HBeAg and loss of HBsAg at 6-12 months of follow-up. In order to obtain an overall measure of treatment efficacy, we calculated the overall risk difference and its 95% confidence interval (95% CI) between frequencies of events in both treated and untreated patients, according to the method of DerSimonian and Laird (36). If the confidence intervals between treated and untreated patients do not overlap, the results are statistically significant. The assumption of heterogeneity implied by the use of random effect models is plausible because of the differences in eligibility criteria, baseline characteristic of patients, treatment modalities and outcome measures. In addition to within-study variance, the random-effects model considers heterogeneity among studies. The overall risk difference was tested for significance using a Mantel-Haenszel $\chi 2$ test (37). We excluded each study at a time to ensure that no single trial would be solely responsible for the significance of any result (so-called robust analysis). All our analyses were computed using a program (courtesy of Professor Joseph Lau, Tufts University, USA). The number of patients needing treatment (NNT) to prevent one event, deriving from the inverse of the risk difference, was given as a measure of treatment effect (38, 39).

Subset 2 included 12 cohort studies (40-51) reporting data on loss of HBsAg, disease decompensation (i.e. ascites, jaundice, encephalopathy, portal hypertensive bleeding, and liver transplantation), development of HCC and death (Table 2). The cohorts of patients in this subset were reviewed to assess the overall likelihood of loss of HBsAg, disease decompensation, development of HCC and death by the Confidence Profile Method (52) using the Fast*Pro software (53). This is a bayesian method for combining evidence ("meta-analysis") to estimate a probability distribution for a parameter. The result is a posterior distribution for the parameters of interest.

## EVALUATION OF AVAILABLE EVIDENCE

When assessing treatment options for chronic hepatitis B, some important issues must be addressed.

### 1. What effects has IFN therapy of chronic hepatitis B on "surrogate" markers of response?

The 24 RCTs included a total of 1299 patients, 444 not receiving any active treatment. Overall, IFN treatment had a favourable, statistically significant effect on all 4 end points in comparison to no treatment. Meta-analysis showed the following risk differences, all in favour of IFN:

- persistent ALT normalization (fig. 1): + 26.2% (95% CI 18.3%-34.0%, $p < 0.00001$); NNT 3.8
- clearance of HBeAg (fig. 2): + 24.3% (95% CI 8.3%-30.4%, $p < 0.00001$); NNT 4.1
- sustained loss of HBV-DNA (fig. 3): + 23.4% (95% CI 17.9%-28.8%, $p < 0.00001$); NNT 4.3
- clearance of HBsAg (fig. 4): + 5.6% (95% CI 3.5%-7.6%, $p < 0.00001$); NNT 18.

Few RCTs were planned to assess the effects of IFN on liver histology. In these RCTs (19, 21, 22, 27) , an histologic improvement was observed. However, the histologic approach to the evaluation of IFN response in chronic hepatitis B has several important limitations and sources of bias:

- the histological picture of chronic hepatitis B is mild to moderate in most cases. Therefore, the relatively small change induced by IFN can be difficult to assess with accuracy and reliability
- many factors might influence the interpretation of histology: inconsistency in the definition of pathological features, technical processing of the specimens, sampling variation

- none of the trials reported a preliminary assessment of the intra/interobserver variations inherent to the semiquantitative evaluation of histological lesions. This can be a particularly important source of bias in cooperative studies, or in studies where the biopsy specimens were observed by different pathologists
- the biopsy specimens reflect just one time-point in a long-term dynamic process, developing at variable speed.

Taking these limitations into account, we regard the IFN-induced histologic changes reported as an approximate, although important, indication of treatment effect, far from being a precise quantitative estimate. Significant histological improvement was usually observed among patients who normalized ALT and cleared serum HBV-DNA, but complete healing of liver lesions was only seen among subjects rebiopsied after many years from seroconversion (41, 47, 51, 54, 55). Many of these had also lost serum HBsAg.

An alternative approach to chronic HBV infection is based on the induction of a brief period of immunosuppression by steroids (56-57), then a withdrawal to provoke an abrupt ALT elevation due to the host immune reconstitution, and a subsequent decline of HBV-DNA. IFN administration is then started 2-4 weeks after stopping steroids. The sequential schedule has been studied in some RCTs and their results have been pooled in a meta-analysis (58). The overall rate of HBeAg loss in 7 RCTs was comparable between the prednisone-IFN and IFN monotherapy groups (41% vs. 35%, OR 1.20; 95% CI, 0.8-1.7). Similar results were observed for sustained ALT normalization (44.5% vs. 38%; OR, 1.19; 95% CI, 0.6-2.0). Analysis of HBeAg clearance stratifying the patients according to pre-treatment ALT levels showed that prednisone-IFN treated cases had a significantly higher proportion of clearance (47.9% vs. 18.4%, $p < 0.01$) only when ALT were low before starting therapy. Even if there could be an advantage in pre-treatment with steroids of this subset of patients, this must be balanced against the risk of flare of liver disease after steroid withdrawal. A severe, often fatal "seroconversion hepatitis" has been in fact reported in subjects with pre-existing cirrhosis (59,60).

The amount of IFN used was clearly an important point. Subjects receiving a total dose of < 200 MU had a 1.37 odds ratio (OR, 95% CI 0.95-1.98) of HBeAg clearance above controls, while those who received >200 MU had an OR of 2.05 (95% CI 1.5-2.78) (61, 62).

Overall experience suggests that the optimal cost-effectiveness ratio on surrogate end-points is reached by treating HBeAg positive patients with 9-10 MU IFN tiw for 4 to 6 months. Predictive factors of a favourable response (8, 9, 28, 29, 25, 63, 64, 56) are:

- low serum HBV-DNA (< 100 pg/ml)
- low amounts of HBcAg in the liver
- high levels of ALT
- high HAI grade at biopsy
- infection in the adult age and/or a history of acute hepatitis
- non-Asian ethnic origin.

**2. What are the long-term benefits of IFN treatment for chronic hepatitis B?**

The clinical course and outcome of patients enrolled in studies in subset 2 is shown in Table 2. The 12 studies (11 prospective and 1 retrospective) included a total of 1975 patients, 1210 not receiving active treatment. Length of follow-up ranged from 2.1 to 8.9 years (mean 6.1).

Meta-analysis showed the following distribution of probabilities:

- Loss of HBsAg (fig. 5): treated 11.4% (95% CI 9.1%-13.7%), controls 2.6% (95% CI 1.8%-3.4%); RD 8.8; NNT 11.4;
- Disease decompensation (fig. 6): treated 9.9% (95% CI 7.7%-12.1%), controls 13.3 % (95% CI 10.1%-16.4%);
- Development of HCC (fig. 7): treated 1.9% (95% CI 0.8%-3.0%), controls 3.16% (95% CI 1.8%-4.5%);
- Liver-related death (fig. 8): treated 4.9% (95% CI 3.3%-6.5%), controls 8.7 % (95% CI 6.1%-11.3%);

The rate of clearance of HBsAg in untreated patients was generally low, and a statistically significant advantage was observed for IFN-treated patients. HBsAg clearance was seen mostly among subjects infected as adults, among those with more active disease at onset, and on average 2 to 4 years after HBeAg/HBV-DNA clearance.

Data on the protective effects of IFN against development of HCC are less encouraging: studies show a strong heterogeneity, which makes the reliability of conclusions of individual studies questionable. On this basis, there is no firm ground to recommend IFN to prevent HCC in HBV-related cirrhosis. It has been suggested from retrospective and prospective studies that IFN treatment might have a protective effect against HCC development in patients with chronic HBV infection independently from viral clearance or resolution of necroinflammation (65). Obviously, IFN-induced viral clearance remains a major outcome for patients with HBV-related chronic liver disease and indirectly reduces the risk of cancer. Some cases of HBV-associated HCC are observed in the absence of cirrhosis (mostly young males with perinatal infection), and have a very aggressive clinical course. No information on the effectiveness of IFN in preventing this subtype of HCC can be gathered from the available studies.

All the data on disease events (i.e liver decompensation and HCC) and on liver-related mortality coming from studies with prolonged follow-up must be considered with caution, since possible biases can originate errors in estimates through:

- data collected from both prospective and retrospective studies conducted in tertiary care centres with limited generalizability
- lack of randomization reducing the internal and the external validity of the studies
- heterogeneity of patients enrolled, both in respect of clinical and demographic features and of possible co-factors
- slow and prolonged course of the disease not allowing an inception cohort;
- few clinically relevant events, relatively small sample size and duration of follow-up less than 8-10 years
- high mortality from non-hepatic causes
- selection and increased surveillance for cases with more severe disease and unfavourable course
- progressive shift over the years of the global spectrum of the disease due to intervening factors (e.g. new diagnostic tests and screening programs; new treatments).

Overall, IFN treatment had a favourable, statistically significant effect only on loss of HBsAg in comparison to no treatment. In contrast, IFN treatment has failed to show statistically significant effects on disease decompensation, development of HCC and liver-related death, albeit favorable trends for all these points are observed.

**CONCLUSIONS**

The available evidence from RCTs or cohort studies of alfa-IFN treatment for chronic HbeAg positive hepatitis B is sufficient to conclude that:

- IFN therapy significantly improve clearance of HbeAg (NNT 4.1) and loss of HBV-DNA (NNT 4.3) compared with no treatment
- The rate of clearance of HBsAg is significantly higher in the IFN treated than in untreated patients (NNT 17.8 ). The magnitude of the overall effect is small but clinically relevant
- There is no clear evidence of a protective effect of IFN against HCC
- IFN treatment could help to delay or prevent disease decompensation and liver-related deaths, but further large-scale, multicenter longitudinal studies are needed to prove this point.

**FIGURE LEGENDS**

Fig. 1. Meta-analysis of IFN therapy for HBeAg positive chronic hepatitis B: effect of treatment, measured as risk

difference, on sustained ALT normalization.

Fig. 2. Meta-analysis of IFN therapy for HBeAg positive chronic hepatitis B: effect of treatment, measured as risk difference, on HBeAg clearance.

Fig. 3. Meta-analysis of IFN therapy for HBeAg positive chronic hepatitis B: effect of treatment, measured as risk difference, on HBV-DNA loss.

Fig. 4. Meta-analysis of IFN therapy for HBeAg positive chronic hepatitis B: effect of treatment, measured as risk difference, on loss of HBsAg.

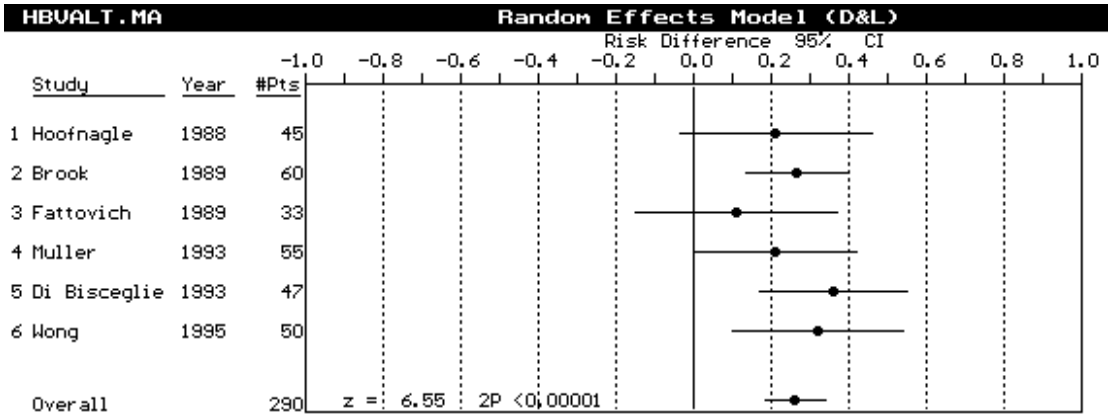
Fig. 5. Probability distribution of the loss of HBsAg rate in HBeAg positive chronic hepatitis B from IFN treated (T) patients and controls (C). Data from cohort studies.

Fig. 6. Probability distribution of disease decompensation rate in HBeAg positive chronic hepatitis B from IFN treated (T) patients and controls (C). Data from cohort studies.

Fig. 7. Probability distribution of development of HCC rate in HBeAg positive chronic hepatitis B from IFN treated (T) patients and controls (C). Data from cohort studies.

Fig. 8. Probability distribution of liver-related mortality rate in HBeAg positive chronic hepatitis B from IFN treated (T) patients and controls (C). Data from cohort studies.

# Persistent ALT normalization




**Favors Control** **Favors Treated**

**Fig 1**

# Clearance of HBeAg

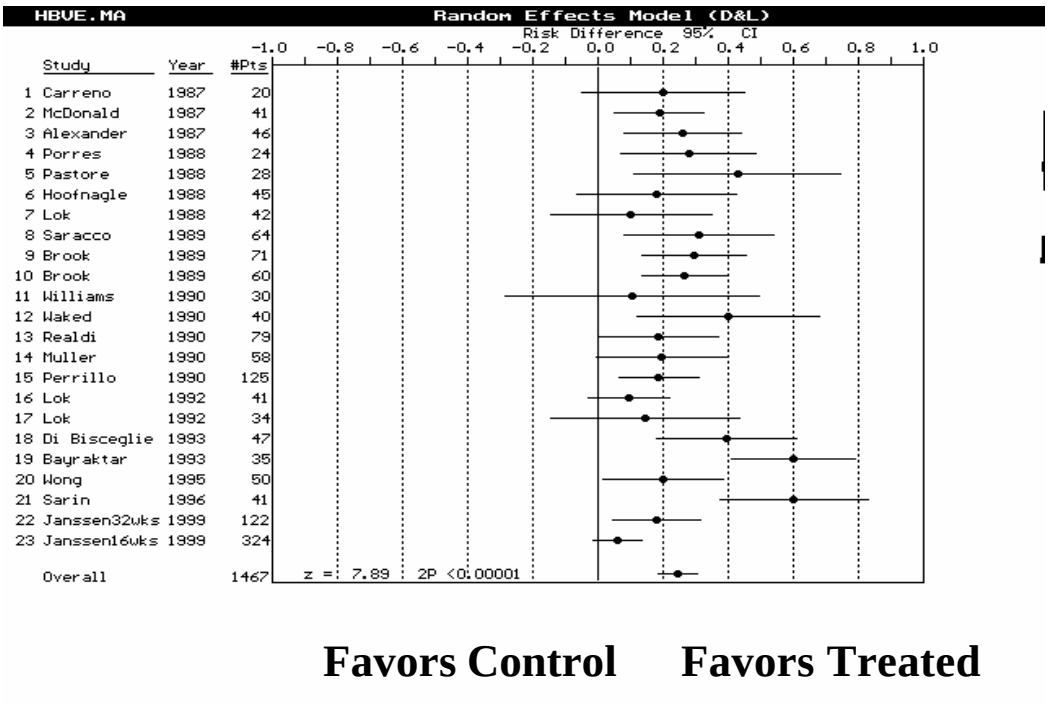



**Fig 2**

# Sustained loss of HBV-DNA

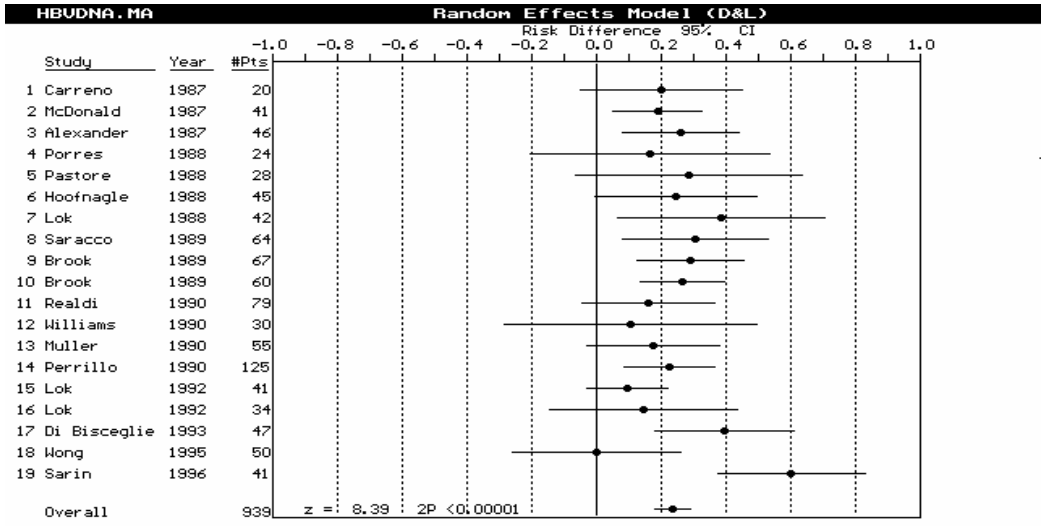
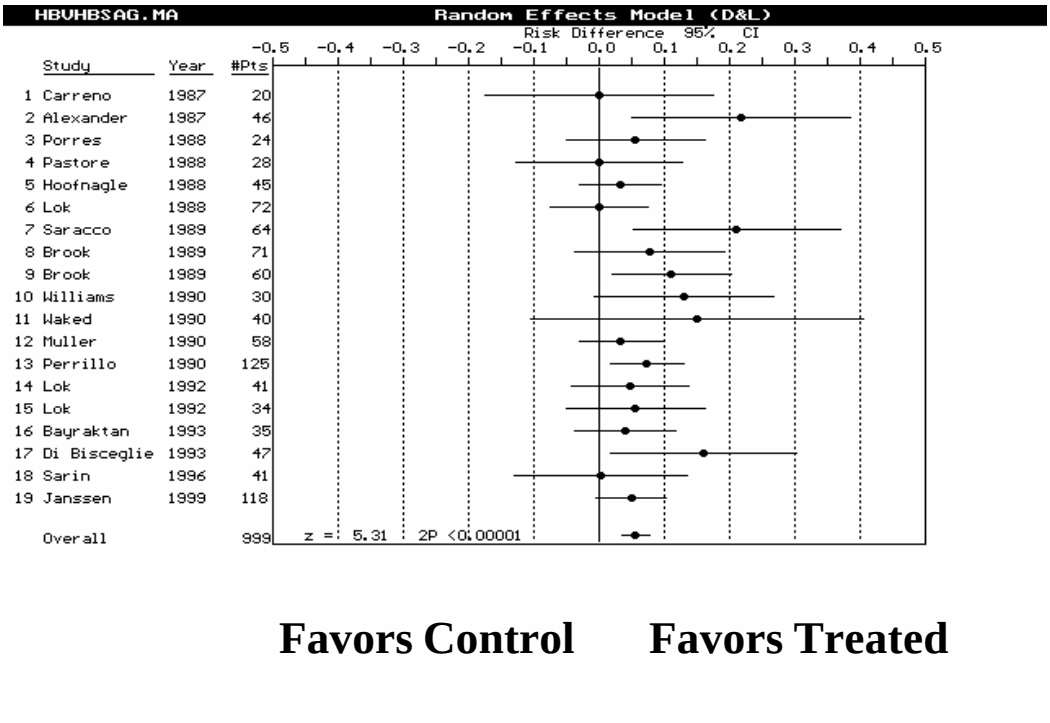



**Fig 3**

# HBsAg Clearance




**Favors Control** **Favors Treated**

**Fig 4**

# Loss of HBsAg

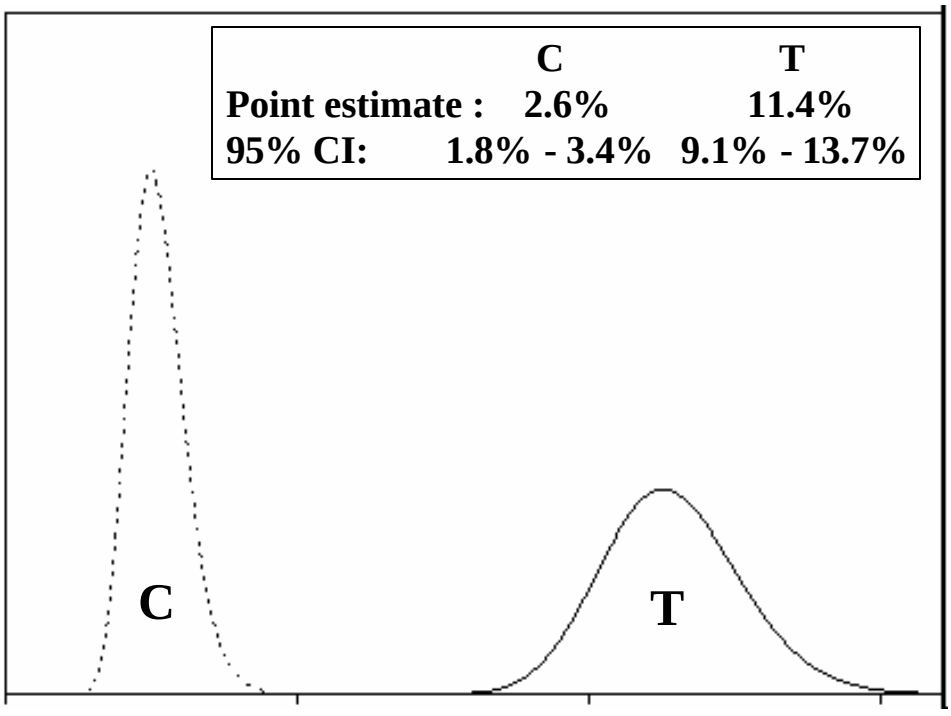



**Fig 5**

# Disease decompensation

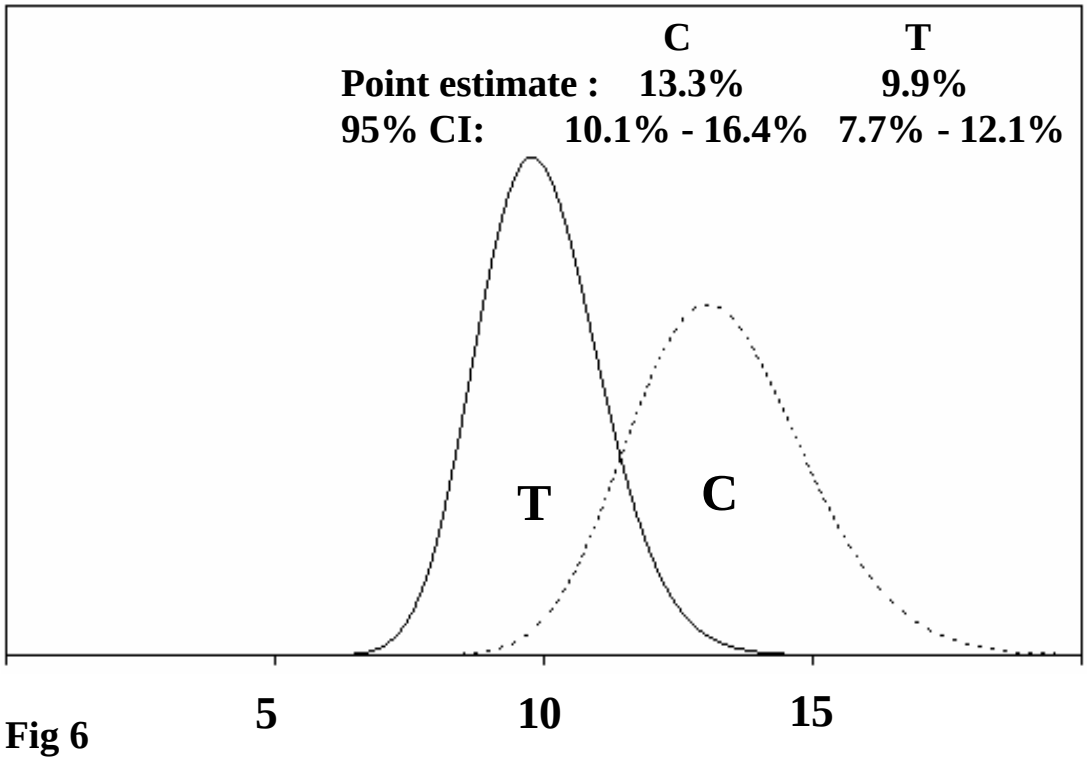



Fig 6

# Development of HCC

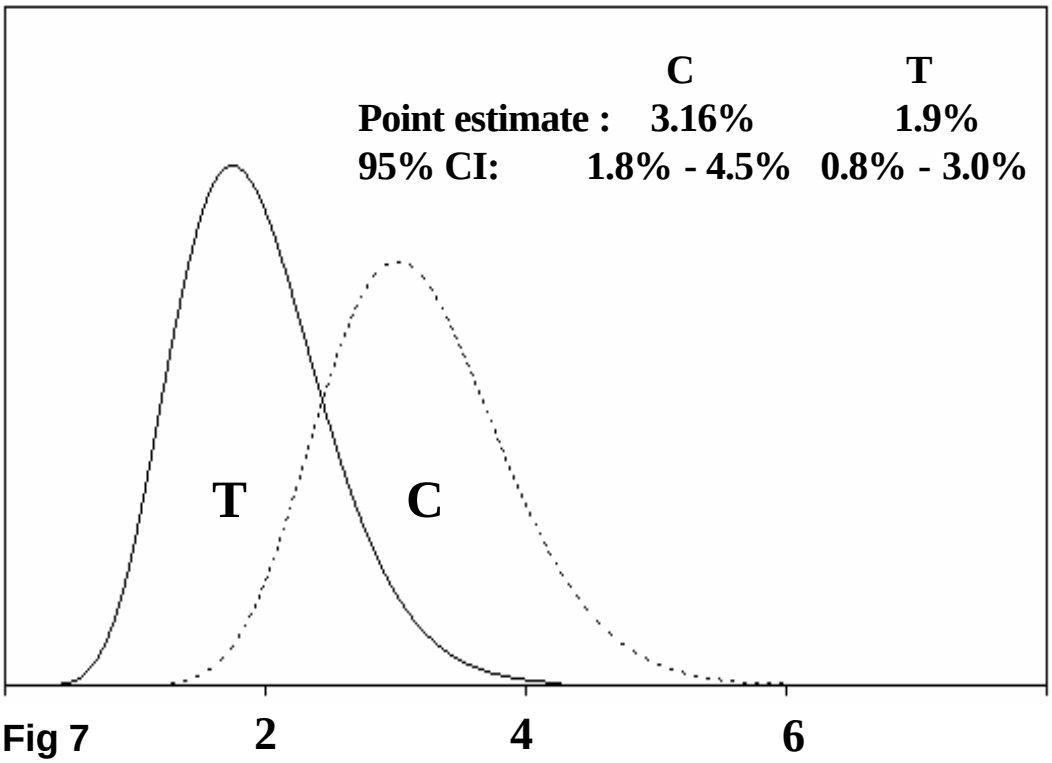



Fig 7

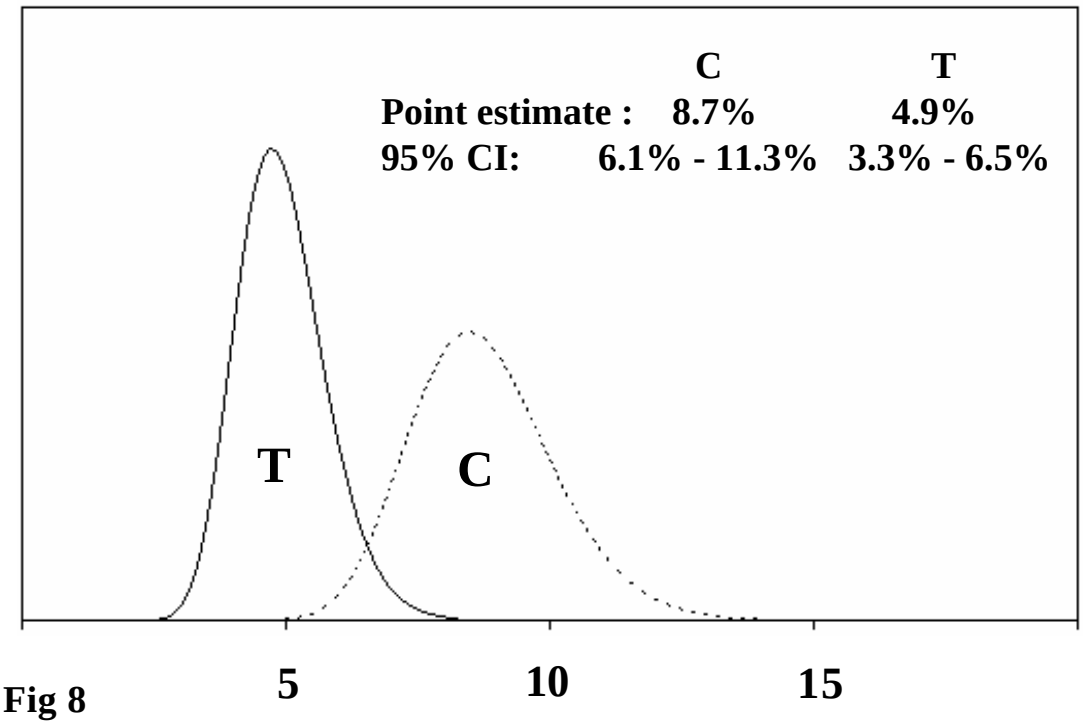



**Fig 8**

Table 1. IFN treatment of HBeAg positive chronic hepatitis B (RCTs)

| *ID* | *Study* | *Year* | *Patients* | *Schedule* | *Total Dose* | *Type of IFN* |
|---|---|---|---|---|---|---|
| ***1*** | Alexander (13) | 1987 | 46 | 10 MU/m2 TIW for 6 months | 720 MU | Lymphoblastoid |
| ***2*** | Carreno (14) | 1987 | 20 | 5.5 MU/m2 IM daily for 3 weeks then twice weekly for 6 months | 380 MU/m2 | r-IFNα-2c |
| ***3*** | Mc Donald (15) | 1987 | 41 | 2.5, 5, 10 MU/m2 IM TIW for 6 months | 180, 360, 720 MU | r-IFNα-2a |
| ***4*** | Hoofnagle (16) | 1988 | 45 | 5 MU daily or 10 every other day for 4 months | 560 MU | r-IFNα-2b |
| ***5*** | Lok (17) | 1988 | 72 | 2.5, 5, 10 MU/m2 IM TIW for 6 months | 180, 360, 720 MU | r-IFNα-2a |
| ***6*** | Porres (18) | 1988 | 24 | 2.5, 5, 10 MU/m2 IM TIW for 6 months | 180, 360, 720 MU | r-IFNα-2a |
| ***7*** | Pastore (19) | 1988 | 28 | 0.07 to 0.10 MU/Kg IM daily for 1 month then twice weekly for 2 months | 2.52 to 3.6 MU/Kg | Leucocyte |
| ***8*** | Brook (20) | 1989 | 60 | 10 MU/m2 TIW IM for 6 months | 720 MU | r-IFNα-2a |
| ***9*** | Brook (21) | 1989 | 71 | 2.5, 5, 10 MU/m2 IM TIW for 6 months | 180, 360, 720 MU | r-IFNα-2a |
| ***10*** | Saracco (22) | 1989 | 64 | 5 MU/m2 IM TIW for 6 months | 360 MU | Lymphoblastoid |
| ***11*** | Fattovich (23) | 1989 | 33 | 4.5 MU IM TIW for 4 months | 216 MU | r-IFNα-2a |
| ***12*** | Muller (24) | 1990 | 58 | 3 MU SC TIW for 4 months | 144 MU | r-IFNα-2b |
| ***13*** | Perrillo (25) | 1990 | 125 | 1 or 5 MU, SC daily for 4 months | 112 or 560 MU | r-IFNα-2b |
| ***14*** | Williams | 1990 | 30 | 2.5, 5, 10 MU/m2 IM | 180, 360 | r-IFNα-2a |

| | | | | | | |
|---|---|---|---|---|---|---|
| ***14*** | Williams (26) | 1990 | 30 | 2.5, 5, 10 MU/m2 IM TIW for 6 months | 180, 360, 720 MU | r-IFNα-2a |
| ***15*** | Waked (27) | 1990 | 40 | 5 MU/m2 SC 3 or 7 times weekly for 4 months | 240 or 560 MU/m2 | r-IFNα-2b |
| ***16*** | Realdi (28) | 1990 | 79 | 4.5 MU IM TIW for 4 months | 216 MU | r-IFNα-2a |
| ***17*** | Lok (29) | 1992 | 34 | 10 MU SC TIW for 4 months | 480 MU | r-IFNα-2b |
| ***18*** | Lok (29) | 1992 | 41 | 10 MU SC TIW for 4 months | 480 MU | r-IFNα-2b |
| ***19*** | Di Bisceglie (30) | 1993 | 47 | 10 MU SC TIW for 4 months | 480 MU | r-IFNα-2b |
| ***20*** | Bayraktar (31) | 1993 | 35 | 5 MU TIW SC for 6 months | 360 MU | r-IFNα-2b |
| ***21*** | Muller (32) | 1993 | 55 | 3 MU SC TIW for 4 months | 144 MU | r-IFNα-2b |
| ***22*** | Wong (33) | 1995 | 50 | 10 MU/m2 TIW for 3 months | 360 MU | r-IFNα-2 |
| ***23*** | Sarin (34) | 1996 | 41 | 3 MU SC TIW for 4 months | 144 MU | r-IFNα-2b |
| ***24*** | Janssen (35) | 1999 | 162 | 10 MU SC TIW for 4 or 8 months | 480 or 960 MU | r-IFNα-2b |

Table 2. Long-term follow-up of IFN treated and untreated patients with HBeAg positive chronic hepatitis B

| *Study* | *Year* | *Follow-up (yrs)* | *Race (Asian/ White)* | *Age (mean yrs)* | *Patients* | *IFN treated* | *Controls* | *HBsAg loss* | *Decompensation* | *HCC* | *D* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Niederau (40)*** | 1996 | 4.2 | W | | 156 | 103 | 53 | 10/103<br>0/53 | 16/103<br>13/53 | | 6/<br>3/ |
| ***Lin (41)*** | 1999 | 7 | A | 32 | 101 | 67 | 34 | 0/67<br>0/34 | 6/67<br>5/34 | 1/67<br>4/34 | 1/<br>4/ |
| ***Fattovich (42)*** | 1997 | 7.2 | W | 46 | 90 | 40 | 50 | 11/40<br>5/50 | 6/40<br>11/50 | 4/40<br>6/50 | 8/<br>1 |
| ***Di Marco (43)*** | 1999 | 7.8 | W | 33.5 | 93 | 39 | 54 | 4/39<br>0/54 | 8/39<br>11/54 | | 3/<br>8/ |
| ***Yuen (44)*** | 2001 | 8.9 | A | 27.5 | 411 | 208 | 203 | 5/208<br>1/203 | 4/208<br>2/203 | 5/208<br>0/203 | 2/<br>0/ |
| ***Chen (45)*** | 1999 | 5 | W | >18 | 25 | 13 | 11 | 3/13<br>0/11 | | | |
| ***Evans (46)*** | 1997 | 2.1 | A | 5-50 | 454 | 0 | 0 | 2/49 | | | |
| ***Korenman (47)*** | 1991 | 4.4 | W | 40 | 64 | 64 | 23 | 13/20<br>10/23 | | | |
| ***Lok (48)*** | 1993 | 6 | A | 19-46 | 128 | 128 | 0 | 2/128 | 3/128 | 0/128 | 1/ |
| ***Lau (49)*** | 1997 | 6.7 | W | 41.5 | 103 | 103 | 0 | 34/103 | 24/103 | 0/103 | 1 |
| ***Fattovich (50)*** | 2000 | 5.5 | W | 47 | 45 | 0 | 45 | | 11/45 | 3/45 | 9/ |
| ***Hsu (51)*** | 2002 | 8.6 | A | 32 | 283 | 0 | 283 | 12/283 | | 6/283 | |

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