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Relation between treatment efficacy and cumulative dose of alpha interferon in chronic hepatitis B

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Background/Aims: **Alpha interferon (IFN) is an established treatment of chronic hepatitis B. The effect has been shown to be dose related, recommended dose regimens being associated with a doubling of the spontaneous, baseline HBeAg to anti-HBe seroconversion rate. However, the efficacy of IFN treatment in relation to the dose of IFN actually received remains to be established. The aim of this study was to estimate the relative efficacy of IFN as a function of the cumulative IFN dose. In addition we determined if and when a patient returns to his baseline chance of seroconversion after stopping IFN therapy.**

Materials and Methods: **Individual patient data from 10 clinical controlled trials were available for the present analysis, in all, 746 patients, of whom 491 received IFN and 255 were untreated controls. The data were analyzed performing a *time-dependent* Cox regression analysis of the relative efficacy of IFN using the cumulative IFN dose administered up to any given time during the observation period and the time after termination of therapy as explanatory variables.**

Results: **In the proposed model, the chance of HBeAg disappearance for a treated patient relative to no therapy was estimated to 2.1 at a cumulative dose of 100 MU and leveled out at about 2.8 at a cumulative dose of 500 MU. The effect of IFN was shown to decay rapidly after discontinuation and after 3 months a patient could be considered to be back to his baseline chance of HBeAg disappearance. These findings show that IFN administered at a dose of 15–30 MU/week should be considered effective (relative efficacy≈2) already after 1–2 months of treatment.**

Conclusions: **The present findings do not lend any support to the concept that IFN treatment becomes less effective when a certain total dose of IFN has been administered or that the treatment effect reaches beyond 3 months after stopping IFN.**

Key words: **Chronic hepatitis B; Cox regression analysis; Interferon treatment; Meta-analysis; Randomized clinical trials; Time-dependent covariates.**

ALPHA-INTERFERON (IFN) treatment of chronic hepatitis B (CHB) introduced more than a decade ago is now an established therapy for this disease (1–5). Short-term response to treatment is evaluated by assessment of serum markers of viral replication, HBeAg disappearance being a simple and widely used response variable. A number of controlled studies have shown that IFN treatment is associated with HBeAg disappearance in approximately 35% of treated patients (6,7). In a recent meta-analysis of individual patient data from 10 clinical controlled trials we showed that IFN treatment overall increased the HBeAg disappearance rate by 1.8 and that the effect was significantly higher in patients treated with higher total doses of IFN (>200 MU/m^2) compared to that observed in patients receiving lower total doses of IFN, i.e. there was a dose response effect of treatment (8). That analysis applied the *time-fixed* (or *time-independent*) Cox regression model assuming that the efficacy of IFN treatment was constant

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throughout the observation period. Moreover, the analysis was performed on an intention to treat principle. Accordingly, the study dose referred to the total scheduled dose, not to the dose actually received by the individual patient. However, the relation between the therapeutic efficacy and the actually received (cumulative) dose of IFN may be of special interest since some patients were withdrawn during treatment or had their scheduled IFN dose modified considerably due to adverse effects and because IFN treatment was often continued for some time after response to treatment.

The present study is a re-analysis of the data (8) performing a *time-dependent* Cox regression analysis of the relative efficacy of IFN using the cumulative IFN dose administered up to any given time during the observation period and the time after termination of therapy as explanatory variables. This was done in order to answer the following questions: (i) what is the relation between the cumulative IFN dose and the relative treatment efficacy and how can this relation best be modeled? (ii) What is the magnitude of the treatment effect following the discontinuation of IFN and when is a patient back to his baseline chance of HBeAg disappearance once IFN has been stopped?

Patients

Individual patient data from previously published and unpublished randomized clinical trials on IFN treatment in patients with chronic HBsAg and HBeAg positive hepatitis were analyzed (9–17). The written consent to use the data for the meta-analysis was obtained from the principal investigators of each of the included trials. The data were kindly provided on data discs by the medical companies sponsoring the trials (Wellcome, Hoffman LaRoche, Schering Plough Int.).

Data from a total of 10 trials were made available. Eight trials compared IFN treatment to no treatment and three of the studies also included different IFN dose levels. Two studies did not include an untreated group; one compared two different durations of IFN treatment and the other study compared IFN treatment

TABLE 1

Alpha interferon treatment regimens, actual total interferon doses and actual duration of treatment in ten randomized trials on alpha interferon treatment of chronic hepatitis B

Study	Treatment arms	No. of patients analyzed	IFN dose (MU)	Frequency	Duration (weeks)	Actual total dose median (range) (MU)	Actual duration weeks (range)
	ARA-AMP	–					
1	IFN	16	7.5–10.0/m^2	TIW	12	601 (333–844)	11 (5–12)
	No Rx	39					
2	IFN	48	2.5–5.0/m^2	TIW	26	705 (36–1055)	25 (1–29)
	No Rx	10					
3	IFN	8	2.5–7.5/m^2	Daily	4	189 (103–374)	4 (3–4)
	IFN	20	5.0–10.0/m^2	TIW	12	529 (214–801)	12 (9–12)
4	IFN	21	5.0–10.0/m^2	TIW	24	778 (333–1103)	20 (11–24)
	No Rx	29					
5	IFN	23	–10.0/m^2	TIW	25	531 (126–783)	26 (4–26)
	No Rx	30					
6	IFN	34	5.0–10.0/m^2	TIW	12	657 (194–781)	12 (12–14)
	No Rx	14					
	Steroid IFN	15	5.0	Daily	16	560 (280–585)	16 (14–22)
	Placebo IFN	13	5.0	Daily	16	560 (90–560)	16 (4–17)
7	Placebo IFN	14	1.0	Daily	16	112 (112–124)	16 (16–21)
	No Rx	41					
	IFN	43	2.5/m^2	TIW	12–24	299 (119–449)	23 (11–27)
	IFN	48	5.0/m^2	TIW	12–24	590 (266–864)	24 (11–31)
8	IFN	42	10.0/m^2	TIW	12–24	1224 (147–1613)	24 (6–27)
	No Rx	41					
	IFN	50	1.5	TIW	16	72 (2–90)	16 (1–20)
9	IFN	43	18.0	TIW	16	864 (18–1044)	16 (1–22)
	No Rx	51					
10	INF	53	4.5	TIW	16	216 (184–234)	16 (14–20)

No Rx: No treatment=untreated controls.
TIW: Thrice weekly.
Actual total dose: total dose of interferon administered to individual patients.
Actual total duration: duration of interferon therapy in individual patients.

with treatment with adenosine arabinoside monophosphate (ARA-MP). Details for each study on scheduled IFN dose, frequency of administration, duration of treatment as well as actual dose and actual duration of treatment are summarized in Table 1.

Positive HBeAg was an inclusion criterion in all studies and in 8 studies active viral replication was ascertained by a positive test for HBV DNA or DNA polymerase activity. Histological entry criteria varied from minimal hepatitis/minor changes to a diagnosis of chronic active hepatitis. Histological evidence of cirrhosis was an exclusion criterion in three studies.

Serological tests for hepatitis D virus (HDV) were performed in four trials, a positive result being reason for exclusion. Human immunodeficiency virus (HIV) antibody testing was originally carried out in two trials (9 and 10), a positive test leading to exclusion. HIV data were later made available by retrospective testing in another two trials (6 and 8).

Of a total of 887 patients randomized, 746 were eligible for the present study. One hundred patients had been excluded prior to analysis of individual trials. The reason for exclusion was in most cases violation of the entry criteria. An additional 41 patients were not included in the analysis: 29 patients who received ARA-AMP, and 12 patients in whom information on HBeAg status and dose regimen was incomplete.

The median age was 36.3 years (range: 10–76 years), 123 (17%) were females and among the 621 males, 183 (30%) were registered as homosexuals.

The majority of patients were Caucasians, 76 were of Asian ethnic origin, 10 were blacks and 13 were "non-specified" non-Caucasians. Only 22 patients were registered as having current or previous intravenous drug abuse. HIV status was ascertained in 348 patients: 25 turned out to be positive, of whom 22 were male homosexuals.

Methods

The endpoint was HBeAg disappearance. In the various analyses the number of days from entry until end point or censoring (i.e. the patient is lost to follow-up without having reached the endpoint) was used as the response variable. The analysis was limited to a maximum of 3 years of follow-up and carried out using a Cox regression model with time-dependent covariates including the cumulative IFN dose administered up until any given time during the observation period and the time after termination of therapy (18,19).

From the available data it was possible to calculate the cumulative dose of IFN up to any time within the treatment period. For patients without entries at certain time points, cumulative dose was obtained by interpolation.

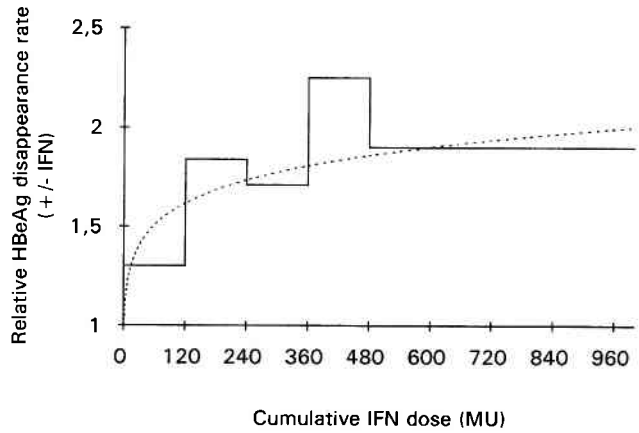

Fig. 1. Relative HBeAg disappearance rate (+/– alpha interferon) in strata defined by the cumulative IFN dose (solid line) and alpha interferon effect described by a one-parameter model (logarithm to cumulative IFN dose) (dotted line).

The analysis was carried out as a stratified survival analysis with each trial as a stratum. This approach takes into account that the response rate may vary for individual patients due to differences in patient population, design and execution of individual studies. The approach also assumes that the effect of treatment or any other variable is independent of the stratum (trial).

The strategy was as follows:

First we studied the association between the HBeAg disappearance rate and the cumulative IFN dose, comparing the HBeAg disappearance rate (IFN/no treatment) in six arbitrary cumulative IFN dose intervals. Based upon the findings of this model we proceeded with a "logarithmic" model, where the relative HBeAg disappearance rate depended on the logarithm of the cumulative IFN dose, ending up with a final "logarithmic" model incorporating the current cumulative IFN dose and the time after termination of therapy.

Results

The result of a time-dependent Cox regression analysis of the relative treatment efficacy in 6 cumulative dose intervals (step function) is illustrated in Figure 1 and described in the appendix. It appears that with increasing cumulative dose up to about 480 MU the HBeAg disappearance rate increased. Cumulative doses above 480 MU did not increase treatment efficacy further. Similar results were obtained with other dose intervals. The shape of the step function (Fig. 1)

suggested that the relative treatment efficacy could best be described by the logarithm of the cumulative IFN dose. The results of a model using logarithmic scoring of the cumulative IFN dose is also illustrated in Fig. 1 for comparison with the step function model and further explained in the Appendix. It can be seen (Fig. 1) that the two curves agreed fairly well and that the relative efficacy of IFN increased rather rapidly and leveled out at a cumulative dose of about 500 MU.

Models using other specifications of the effect of the cumulative IFN dose (including a piecewise linear relation) did not provide a better fit to the data (results not shown).

Since this logarithmic model unrealistically assumed that the treatment effect persists after stopping treatment it needed to be supplemented with a term modeling the treatment effect after IFN discontinuation. Thus, the final model included the following two time-dependent terms: an ascending part $z_1(t)$, reflecting the cumulative IFN dose and a descending part, $z_2(t)$, reflecting time after treatment stop (and total IFN dose). The exact definition of these terms is given in the Appendix. Here it suffices to note that the modeling included a time interval Δ, after the treatment was stopped, where the relative treatment effect was allowed to decrease, and a level for the relative treatment efficacy Δ days after the treatment was stopped. In this model three basic questions were relevant: (i) Does the relative treatment effect increase with increasing cumulative IFN dose during treatment? (ii) Does the relative treatment effect decrease during the time interval Δ days after treatment is stopped? (iii) Has the relative treatment effect vanished Δ days after treatment is stopped? As explained in the Appendix, our model had parameters β_1, β_2, and $\beta_1+\Delta\beta_2$, which correspond to the three questions. Table 2 shows the results for relevant choices of Δ: 30, 60, 90 and 120 days. It is seen that the answers to the three questions were affirmative for all values of Δ. β_1 was significantly positive and β_2 was significantly negative everywhere , and $\beta_1+\Delta\beta_2$ was significantly different from 0 nowhere. However, the confidence interval for $\beta_1+\Delta\beta_2$ included rather large and clinically significant treatment effects, in particular for small values of Δ. These findings suggested that the effect of IFN disappears within a few months after the treatment has been stopped.

The ascending and descending parts of the model (for Δ=90 days) are shown in Fig. 2. It is seen that the effect of IFN during treatment was larger than in a one-parameter model where the declining effect after last treatment day was not taken into account (cf. Fig.1).

Examples of use of the two-parameter model

In the following examples we have, using the two-parameter model, calculated the relative treatment effect of IFN for a patient during and after IFN treatment. The regression coefficients depend upon the number of days Δ considered for possible residual effect of IFN therapy. In all examples, Δ was set to 90 (days), i.e. we used β_1=0.161 and β_2=–0.0015 (see Table 2 and Appendix).

Example 1:

A patient has received a cumulative IFN dose of 100 MU and is still in treatment (t < last treatment day):
Relative treatment effect (100 MU)=exp(0.161× $\log_e$ 101)=2.10
i.e. at this stage IFN has increased the chance of HBeAg disappearance for that patient by 2.10.

Example 2:

A patient has received a cumulative IFN dose of 500 MU and is still in treatment (t < last treatment day):
Relative treatment effect (500 MU)=exp(0.161× $\log_e$ 501)=2.72.
i.e. at this stage IFN has increased the chance of HBeAg disappearance for that patient by 2.72.

TABLE 2

Regression coefficients for the "ascending" part of the model (β_1), the "descending" (β_2) and the treatment effect after last treatment day + Δ ($\beta_1+\Delta\beta_2$), Δ being 30, 60, 90 and 120 days respectively

	Δ (days)			
	30	60	90	120
β_1 (SE)	0.170 (0.034)	0.163 (0.033)	0.161 (0.033)	0.163 (0.033)
β_2 (SE)	0.0042 (0.0014)	–0.0021 (0.0007)	–0.0015 (0.0005)	–0.0013 (0.0005)
$\beta_1+\Delta\beta_2$ (SE)	0.0437 (0.030)	0.0369 (0.0307)	0.0259 (0.033)	0.0070 (0.036)
$\beta_1+\Delta\beta_2$=0*	p=0.15	p= 0.23	p=0.44	p=0.84

* Wald test.

Example 3:
A patient has received a cumulative IFN dose of 500 MU and treatment was discontinued 80 days ago (t > last treatment day):
Relative treatment effect (500 MU)=exp((0.161×$\log_e$ 501)+(-0.0015×80×$\log_e$ 501))=1.29
i.e. at this time the chance of HBeAg disappearance for that patient has decreased to 1.29 relative to no treatment.

Discussion

In a model evaluating the effect of IFN in different dose intervals relative to no treatment we found (Fig. 1) that the relation between cumulative IFN dose and increase in HBeAg disappearance (relative treatment effect) is probably best modeled by using a logarithmic scoring of the cumulative IFN dose. In order to allow for a decaying effect of IFN once treatment was stopped, we further incorporated into the model a covariate based upon total IFN dose and time after stopping treatment. In our model the relative treatment effect should be interpreted as the rate of HBeAg loss for a treated patient relative to no treatment when the patient undergoing treatment has received a certain cumulative dose of IFN. For a patient who has stopped treatment after having received a certain total dose of IFN, the relative treatment effect is also dependent on the number of days which has elapsed after termination of therapy.

From Fig. 2 and examples 1 and 2 it is seen that the relative treatment efficacy of IFN has an abrupt increase in the dose interval 0–100 MU. Once a total dose of 100 MU is reached, the HBeAg disappearance rate is increased by more than a factor 2, suggesting that our primary analysis (8) underestimated the optimal efficacy of IFN for the individual patient. However, it can also be seen that the increase in HBeAg disappearance rate levels out once a cumulative dose of more than about 500 MU is reached. This means that once a patient with chronic hepatitis B has started treatment with IFN, the increase in HBeAg disappearance reaches a factor 2 relatively early and thereafter slowly increases and approaches a factor 3 when a dose level of 500 MU is exceeded. If the patient receives 5–10 MU thrice weekly the patient will have an increase in HBeAg disappearance rate of 2 after 4–8 weeks. Hereafter the rate will only increase slowly and will have reached 2.7 after 16–32 weeks.

From Fig. 2 and example 3 it is clear that the effect of IFN decays rapidly and that the effect of previous IFN treatment has disappeared within 3 months, at which time the HBeAg disappearance rate will for all practical purposes for the individual patient be the same as before IFN was started.

In our previous analysis we showed that the relative effect of IFN was independent of patient pretreatment variables (8). An analysis of interactions was also performed for the present time-dependent model with a similar result (results not presented). However, the model gives no direct information about the likelihood of response for the individual patient during a certain course of IFN treatment. This likelihood depends both upon the tendency to HBeAg disappearance - which for the individual patient depends upon certain pretreatment variables (8,20–23) - and the time-dependent relative efficacy of IFN treatment.

Although our findings suggest that the relative efficacy of IFN is constant during prolonged treatment it would be hazardous to predict beyond the time frame defined by the duration of treatment employed in the underlying studies i.e. 16–24 weeks. Ideally, the model proposed here should be validated

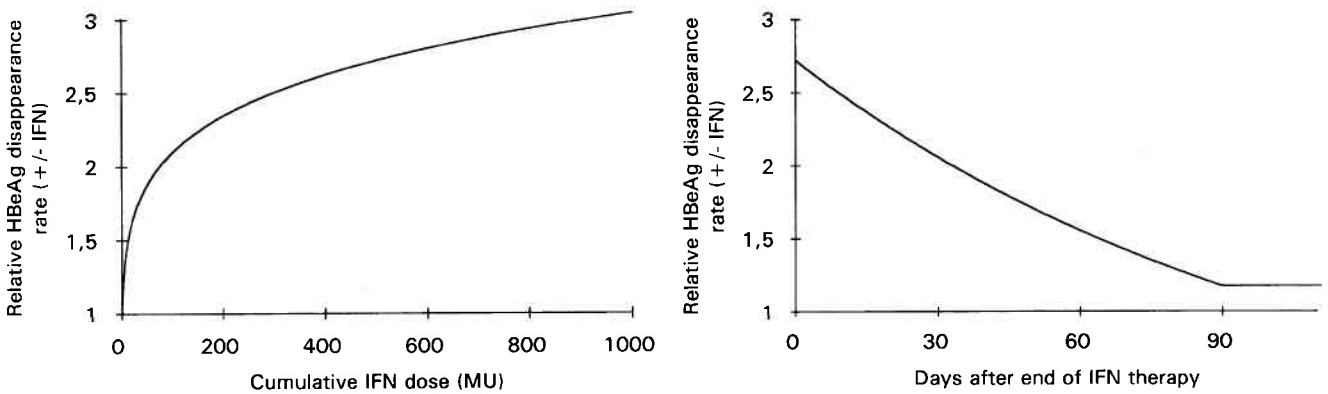

Fig. 2. The "ascending part" and the "descending part" of the relative treatment effect of alpha interferon described by a Cox model with two parameters. The descending part is obtained after a cumulative alpha interferon dose of 500 MU assuming a duration of 90 days of the post-treatment effect (see text).

in another group of patients treated with IFN for chronic hepatitis B. However, apart from the Eurohep database, from which the present data are generated, we are not aware of other relevant, accessible databases.

The present findings show that IFN may be considered effective already after 4 weeks of treatment depending upon dose and that the treatment may still be effective after extended treatment. The present findings do not lend any support to the concepts that IFN treatment becomes less effective when a certain total dose of IFN has been administered or that the effect of IFN treatment reaches beyond 3 months after stopping IFN.

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Appendix

In the Cox model for time-dependent covariates the HBeAg disappearance rate at time t for a patient in trial j will be given by:

$$\lambda(t)=\lambda_{0j}(t)e^{\beta_1 z1(t)+\beta_2 z2(t)+\cdots+\beta_n zn(t)}$$

where $\lambda(t)$ is the HBeAg disappearance intensity of a patient and $\lambda_{0j}(t)$ is the so-called baseline HBeAg disappearance intensity. $\beta_1-\beta_n$ are regression coefficients and $z_1(t)-z_n(t)$ are covariates characterizing the patient and the therapy.

Stepfunction

This model has 6 time-dependent covariates ($z_1(t)$–$z_6(t)$):

$z_1(t)$ = 1 for cumulative IFN dose in first IFN dose interval at time t , otherwise

$z_1(t)$ = 0 and

$z_2(t)$ = 1 for cumulative IFN dose in second IFN dose interval at time t, otherwise

$z_2(t)$ = 0 etc.

and for each of the 6 dose intervals there is a corresponding regression coefficient (β_1–β_6).

The regression coefficients for the dose intervals and the resulting estimated relative treatment effects (step function)

Dose interval	Estimated β (SE)	Relative treatment efficacy	No. of treated patients contributing to relative treatment efficacy
0–120 MU	0.265 (0.226)	1.3	491
120–240 MU	0.608 (0.218)	1.8	419
240–360 MU	0.536 (0.266)	1.7	338
360–480 MU	0.811 (0.270)	2.3	292
480–600 MU	0.642 (0.244)	1.9	266
> 600 MU	0.641 (0.189)	1.9	186

Note that since the cumulative IFN dose is time-dependent, all treated patients contribute to the first dose interval (0–120 MU) while only patients reaching a cumulative dose above 600 MU contribute to the last interval.

One-parameter logarithmic model:

The logarithmic model has only one time-dependent covariate: z (t)=log(cumulative IFN dose(t) + 1) and the corresponding regression coefficient (β).

In the model the regression coefficient was estimated at $\beta = 0.101$ (SE(β) 0.024).

Two-parameter logarithmic model:
In this model, the two time-dependent variables are defined as follows:
The exact definitions of these variables are as follows (t being the current time in days from start of treatment and Δ the maximum duration in days of post-treatment IFN effect specified by the model):

During treatment (t < last treatment day):
$z_1(t) = \log_e$ (cumul IFN dose (t) + 1)
$z_2(t) = 0$

After treatment stop (less than Δ days after treatment stop):
$z_1(t) = \log_e$ (total IFN dose +1)
$z_2(t) = (t -$ last treatment day) $\log_e$ (total IFN dose + 1)

After treatment stop (more than Δ days after treatment stop):
$z_1(t) = \log_e$ (total IFN dose + 1)
$z_2(t) = \Delta \log_e$ (total IFN dose + 1)

The final model for patients in trial j=1, 2,....., 10 had this form:

$$\lambda_j(t) = \lambda_{0j}(t) e^{\beta_1 z1(t) + \beta_2 z2(t)}$$

where $\lambda_j(t)$ is the rate of HBeAg disappearance for a patient at time t in trial j and $\lambda_{0j}(t)$ is the corresponding so-called baseline rate of HBeAg disappearance in trial j and β_1 and β_2 are regression coefficients.
For an untreated patient $z_1(t)$ and $z_2(t)$ are zero and thus $\lambda_j(t) = \lambda_{0j}(t) \times \exp(0) = \lambda_{0j}(t)$.
The relative treatment effect (+/-) IFN is therefore: $\exp(\beta_1 z_1(t) + \beta_2 z_2(t))$, since $\lambda_{0j}(t)$ cancels out.