HIGH-DOSE ALPHA-INTERFERON TREATMENT IN AMYOTROPHIC LATERAL SCLEROSIS

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ABSTRACT

Twenty four patients with the spinal form of amyotrophic lateral sclerosis (ALS), 10 in an open series and 14 in a randomized placebo controlled manner, were treated with a short, single course of the maximum tolerated dose of natural alpha interferon. The drug was administered as a continuous intravenous infusion in the course of four to six days. The doses ranged between 250 and 950 million IU, (a mean of 560 IU). Such high-doses caused notable side-effects which were dose limiting; tiredness and fatigue up to unconsciousness were the most common. Reversible leukopenia was also observed. The mean survival time for interferon-treated patients (N = 19) was 42.6 months, and for placebo-treated patients (N = 5) 30.0 months. These results suggest that the maximum tolerated interferon dose was reached without a notable change in the course of ALS.

Key words: maximum IFN dose

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RESUMEN

Se trataron 24 pacientes con la forma espinal de esclerosis lateral amiotrófica (ALS), 10 en una serie abierta y 14 de forma aleatorizada, controlada, con un ciclo único, corto de la dosis máxima tolerable de interferón alfa natural. La droga se administró en una infusión intravenosa continua durante cuatro a seis días. Las dosis estuvieron entre 250 y 950 millones de UI (promedio 560 millones UI). Dosis tan altas produjeron efectos secundarios notables, que fueron limitantes de la dosis. El cansancio y fatiga hasta la inconsciencia fueron los más frecuentes, así como leucopenia reversible. La supervivencia promedio de los pacientes que recibieron interferón (N = 19) fue de 42,6 meses y la de los que recibieron placebo (N = 5) fue de 30,0 meses. Los resultados sugieren que se alcanzó la dosis máxima tolerable de interferón sin un cambio notable en el curso de la ALS.

Palabras claves: dosis máxima de IFN

Introduction

Amyotrophic lateral sclerosis (ALS) is a crippling and fatal disease with motor neurone wasting and inevitable progression of voluntary muscle weakness. Although known as a clinical entity since the delineation of Charcot, its etiology and pathogenesis still remain unknown. The incidence varies between 0.6 - 2.6 per 100.000 in different studies (1). Various putative causes have been intensively studied. These include genetic components, viruses, endogenous and exogenous toxins, immunologic or other biochemical abnormalities of the neurons and the lack of nerve growth factors. Between 5 and 10 % of ALS patients have a family history and the causative gene has been linked to chromosome 21 (2). A recent study shows that 20 % of the family variant of ALS is associated with defects in the superoxide dismutase gene. The enzyme catalyses the conversion of superoxide to hydrogen peroxide and its malfunction may mediate the motor neuron damage via intracellular accumulation of free oxygen radicals (3). The clinical similarities between ALS and the late post polio syndrome have raised a hypothesis of common viral etiology of these diseases. In a recent study, a positive correlation between previous poliomyelitis and mortality from motor neuron diseases was found (4). However, all attempts to identify a viral antigen or transmissible agent associated with ALS have been unsuccesful so far. Interferons (IFNs) exert antiviral, cytostatic, immunomodulatory and hormone-like effects. They are used for the therapy of certain chronic infections and malignancies, and recently, beta IFN was registered for the treatment of multiple sclerosis. However, it is not known on which of the multiple biological effects of IFNs is their clinical efficacy based. In a preliminary study carried out at the University of Helsinki, treatment of ALS patients with subcutaneous injections of low doses of natural alpha IFN failed to affect the progression of the disease (5).

The present study employed the same IFN, but it was administered as a continuous intravenous infusion at a ca. 50-fold higher daily dose than in the preliminary study. Our group reported that the treatment schedule resulted in measurable IFN levels in the cerebrospinal fluid and in a transient improvement of the hand grip force (6). The present paper reports the clinical course of the patients.

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Patients and Methods

During 1982-90, 24 ALS patients (14 men and 10 women) with spinal onset, were enrolled in the study. The first 10 patients were treated in an open series. The next 14 patients were randomized to receive either IFN (N = 9) or placebo (N = 5). Patient inclusion criteria were as follows: 1) confirmed diagnosis of ALS based on clinical follow-up and electromyography (EMG), 2) spinal onset and symptoms from more than one limb, 3) ambulatory patient at the time of entry, 4) no other concomitant neurological or malignant disease, 5) no diseases which would contraindicate the use of a high IFN dose and 6) under 75 years of age and a score of 70 % or more on the Karnofsky Performance Status Scale (7).

When necessary, myelography, computed tomographic scan or magnetic resonance imaging of the cervical spine were performed to exclude compressive myelopathy and other diseases. Familial forms of ALS and cases with bulbar onset were excluded. All clinical evaluations were performed by the same examiner.

The natural human leukocyte IFN was prepared as described by Cantell K, *et al* (8). The batches contained 15 to 30 x 10^6 IU per mL and their specific activity ranged between 3 and 5 x 10^6 IU per mg of protein. Human serum albumin at the same protein concentration served as the placebo. The drugs were administered as a continuous intravenous infusion over four to six days. The scheduled daily dose was 100 million IU during the first two days and 200 million IU thereafter. Because of severe side-effects the dose had to be reduced in most patients. The patients remained in the hospital for two to eight days after the infusion. Neither the treating physicians and nurses nor the patients knew the true nature of the infusion. Only one member of the research team (MF) was aware of the drug code. The age and clinical status of the patients and the interval from the onset of the disease were comparable in the IFN and placebo groups.

Informed consent was obtained from all the patients and the study was approved by the Ethical Committee of the hospital.

To evaluate the natural course of the disease, an additional reference group was formed by analyzing all death certificates coded under 348 (ICD-8) and 335 (ICD-9) at the Central Statistical Office of Finland during 1978-90. Their total count was 1188. Only cases with ALS as underlying, associated or contributory cause of death were accepted. Cases with bulbar or unspecified onset and familial forms were excluded. The analysis yielded 14 death certificates in which the interval between diagnosis and death was accurately recorded.

Results

All patients completed the study, although IFN dosages had to be reduced in 13/19 of them because of side-effects. In the placebo group, the side-effects were so mild, that dosages were not reduced.

The main dose-limiting side-effects were fatigue in 9/19 (47.4 %) in the IFN group, 2/5 (40 %) in the placebo group and a marked leukopenia (< 2.0) in 8/19 (42.1 %) in IFN group and 0/5 in the placebo group. (Table 1). The maximum tolerated doses ranged from 250 to 950 million IU, and the mean dose given was 560 million IU. The treatment caused relief from spasticity, an increase in muscle force, a diminution in deep tendon reflexes, disorientation, confusion and reversible coma in one case. These effects were short-lasting, from two weeks up to two months. The increase in hand grip force continued up to six months in some patients.

The IFN-treated ALS patients lived longer than the placebo-treated patients. The survival periods of the patients are shown in Tables 1 and 2. Two patients in the IFN group are still alive. All other patients have died and in every case the underlying or associated diagnosis was ALS. Autopsies were not done in all cases, as the repeated ENMG and clinical course were suggestive for ALS.

The IFN therapy did not meaningfully affect the course of ALS, neither did it cure it. The mean survival periods of all IFN-treated patients was 42.6 (SD 32.1) months (Table 1). The mean survival period in the open series was 45.2 months and in the randomized group 39.7 months. The corresponding figure in the placebo group was 30.0 (SD 28.2) months. The difference is not significant, but the placebo group is too small for adequate statistical comparisons. The mean survival period in the reference group was 17.0 months (SD 10.3) (Table 2). The cumulative proportion of the survivors in each group is presented in the survival curves of Figure 1.

Two of the IFN-treated patients were still alive at the selected reference day, and they were included in the analysis as censored cases. The IFN-treated group lived longer than placebo-treated patients, but because of the small size of the placebo group, no statistical significance was reached. As the control group was historical and not randomly included, it is not used in statistical comparisons.

Discussion

The clinical course of high-dose IFN-treated patients resembled encephalitis, and high cerebrospinal fluid IFN concentrations can be considered the main cause of symptoms in encephalitis.

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Table 1. *ALS patients in the interferon and placebo groups.*

A. IFN-treated patients, open series					
Initials	Age (years)	Sex m/f	IFN dose (mili. IU)	Survival (months)	Side-effects (dose limitting)
H. K.	29	f	800	55	tiredness, fatigue
S. L.	38	f	450	72	leukopenia
I. H.	37	f	300	78	leukopenia
E. H.	46	f	600	41	--
I. S.	51	m	950	27	leukopenia
F. E.	65	m	600	3	unconsciousness
E. H.	51	m	250	14	fatigue
J. T.	60	f	650	112+	leukopenia
A. S.	65	m	700	16	--
T. H.	68	f	385	34	leukopenia, fatigue
B. IFN-treated, randomized patients					
M. K.	37	f	620	109+	leukopenia
P. T.	40	f	600	67	--
M. T.	40	m	600	13	--
J. S.	30	m	800	54	--
K. V.	62	m	550	25	fatigue
V. H.	63	m	500	26	fatigue
P. P	63	m	300	16	leukopenia, fatigue
E. S.	56	m	450	20	leukopenia, fatigue
P. S.	53	m	500	27	fatigue
Mean	50.2	8/11	558	42.6	
C. Placebo-treated, randomized patients					
Initials	Age (years)	Sex m/f	Survival (months)	Side-effects (not dose limitting)	
H. S.	43	m	78	fatigue	
P. H.	60	m	21	--	
K. S.	44	m	3	--	
E. N.	62	f	23	fever	
R. S.	57	f	25	fatigue	
Mean	53.2	3/2	30.0		

The main reason for the adopted treatment schedule was to overcome, at least to some extent, the blood brain barrier for IFN. Our group has reported that, by the end of the infusion, the IFN concentration in the cerebrospinal fluid was in the order of 100 IU per mL (6). It was also reported that the high-dose IFN treatment caused a transient increase in the hand grip force of the patients (6). This finding bears a resemblance to the reports of the possible beneficial effects of the thyrotropin-releasing hormone or its analogues on ALS (9-12). Previous studies by our group (5, 6) and by others, have failed to demonstrate an arrest of the progression of ALS by IFN therapy (13, 14). Neither did the IFN therapy cure the patients in this study. However, the present study is the first in which both of the doses are high enough and the follow-up is long enough to allow an analysis of the possible effects of the treatment on the survival of the patients.

The patients in both IFN groups lived longer, on an average, than those in the placebo or control groups, even if the long-time survivors are excluded. In any case, the survival was mainly age-dependent and no clear treatment-associated survival effects could be seen. We are aware of the fact that the mortality is not necessarily an ideal reflection of the progression of ALS since most of the patients die of respiratory failure, which can be affected by the

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treatment. However, none of the patients in any of the groups was in the respirator at the end of the disease. Thus, the artificial prolongation of life did not play a significant role. An attempt was made to homogenize all the three groups of patients by excluding familial and bulbar forms. The highest doses of natural alpha IFN ever given to patients caused high IFN levels in the cerebrospinal fluid; hence, this treatment might affect the process inside the blood brain barrier. The results did not show notable changes in the course of ALS. Blinded studies are difficult (or impossible) to conduct with high-dose IFN because of flu-like side-effects. The effects of IFNs are short-termed. Therefore, it is unlikely that a single course of the treatment may permanently change the course of ALS.

Further studies with lower doses and repeated infusions are needed.

Table 2. *ALS patients in the reference group.*

Initials	Age (years)	Sex m/f	Survival (months)
S. A.	76	f	24
L. K.	76	f	15
T. L.	79	f	17
T. L.	63	f	18
E. M.	68	m	16
R. A.	65	m	7
M. A.	43	m	18.5
A. A.	62	m	16.5
S. H.	69	f	30
R. H.	51	m	16
L. H.	64	f	42.5
L. H.	60	m	5.5
L. K.	71	m	10
A. K.	78	f	2.5
Mean	66	7/7	17.0

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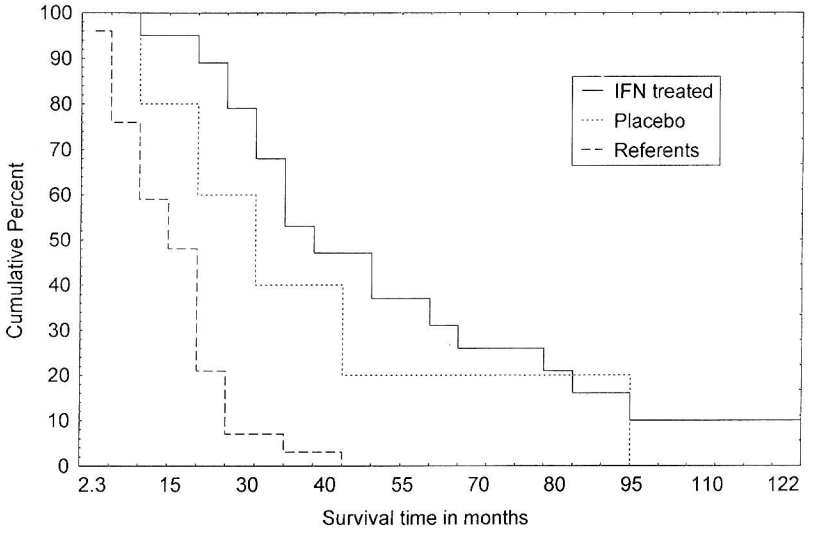

Figure 1. *The cumulative percentage of survivors in the IFN-treated (N = 19), placebo-treated (N = 5), and reference (N = 14) groups during the follow-up.*