Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
MULTICENTRE DOUBLE-BLIND STUDY OF EFFECT OF INTRATHECALLY ADMINISTERED NATURAL HUMAN FIBROBLAST INTERFERON ON EXACERBATIONS OF MULTIPLE SCLEROSIS*

LAWRENCE JACOBS1 ANDRES M. SALAZAR2,3 ROBERT HERNDON4 ARNOLD FREEMAN5 ALBERT CUETTER2 WILLIAM A. SMITH2 ANDRES M. SALAZAR2,3 PETER A. REESE5 RALPH JOSEFOWICZ4 FARHAT HUSAIN2 ROSLYN EKES1 JUDITH A. O'MALLEY5

Dent Neurologic Institute, Millard Fillmore Hospital, and State University of New York School of Medicine at Buffalo, New York, USA;1 Neurology Service, Walter Reed Army Medical Center, Washington, DC;2 Department of Neurology, Uniformed Services University of the Health Sciences, Bethesda, Maryland;3 University of Rochester Medical Center, New York;4 and Roswell Park Memorial Institute, Buffalo, New York5

Summary In this randomised, double-blind, placebo-controlled, 2-year multicentre study intrathecally administered natural human fibroblast interferon (IFN-B) was effective in reducing exacerbations of multiple sclerosis (MS) in patients with exacerbating/remitting disease. The mean reduction in exacerbation rate of 34 patients who received IFN-B (recipients) was significantly greater during the study than that of 35 patients who received placebo (p <0.04). The prestudy exacerbation rates were comparable in recipients and controls, but the rate at the end of the study was significantly lower in recipients than in controls (p <0.001). IFN-B was given by nine or ten lumbar punctures over the first 6 months of the study, and patient observations continued for 2 years. IFN-B was well tolerated in 95% of the recipients, and the side-effects experienced were clearly acceptable for the benefits achieved. Low doses of indomethacin reduced the toxicity of IFN-B and played an important role in successful double-blinding.

Introduction

In 1981 we reported the results of an open preliminary study suggesting that intrathecally administered natural human fibroblast interferon (IFN-B) reduced exacerbations in multiple sclerosis (MS) patients.1,2 The rationale for administering IFN-B to such patients included evidence for a viral and immunopathological aetiology for this disease and the known potent antiviral and immunomodulatory actions of the interferons.3-8 IFN-B was given intrathecally because interferons do not effectively cross the blood-brain barrier to reach the central nervous system (CNS) when administered systemically, but can safely be given intrathecally.8-18

We have since carried out a randomised, double-blind, placebo-controlled, 2-year multicentre study, including 3-5 times as many patients as the preliminary study, to determine definitively whether intrathecally administered IFN-B is beneficial in MS.19 This study was monitored throughout by the United States National Institutes of Health.

Patients and Methods

We studied 69 patients who met the clinical and laboratory criteria for the diagnosis of definite MS.20-22 All had exacerbating/remitting disease (stable or progressive) and high prestudy exacerbation rates (at least 0.6 per year). The prestudy duration of illness was at least 1 year in all but 2 patients (5 months, 10 months), who were included because they clearly had MS (recently revised criteria23) with high exacerbation rates. Each patient underwent a complete neurological examination at the beginning of the study, and the severity of symptoms and signs was scored according to a modified Kurtzke method.24 The prestudy exacerbation rate was determined by dividing the total number of exacerbations (standard definition20-23) recorded before the study by the duration of disease up to the time of randomisation. In the 2 patients who had had MS for less than a year, the number of exacerbations recorded before the study was considered as the number that would have occurred in a full year (ie, we did not adjust their rates upward to compensate for their shorter disease durations). Patients were then randomly assigned (biased coin) to the recipient or control group by means of stratification based on prestudy exacerbation rate (ie, less than two exacerbations/year; two or more exacerbations/year). The randomisation yielded recipient and control populations with similar mean prestudy exacerbation rates (recipients 1.79, controls 1.98 per year). There were no meaningful differences in other clinical parameters between the two groups (eg, age, sex, presudy disease duration, disability status, and functional group scores).

Patients were re-examined regularly or whenever they felt they might be having an exacerbation; exacerbations, clinical disability status, functional group scores, and an overall assessment of the patient's clinical condition (improved, unchanged, worsened) were recorded. Exacerbations were treated by intramuscular or intravenous corticotropin daily for 10 days. Such treatment may limit the severity of symptoms and signs of exacerbations but does not prevent their recurrence.24
Exacerbation rates during the study were calculated from the number of exacerbations occurring during the study and the time on the study. A one-tailed $t$ statistic was used to test the effect of treatment on changes in exacerbation rate. The statistical plan, based on data from our preliminary study, was designed to detect a true difference in exacerbation-rate reductions between recipients and controls of 0.65 exacerbations per year at a type I error level of $0.05$ with a power of 0.80.

The IFN-B used was produced by superinduction of human fibroblast cells at Roswell Park Memorial Institute, Buffalo.1,2 The preparation had a specific activity of $1 \times 10^7$ interferon reference units of IFN-B per mg protein. It was the same type as that used in the preliminary study and had passed the toxicity and safety tests required by the Food and Drug Administration (FDA IND no 1325).

IFN-B was given to the recipients by serial lumbar punctures carried out weekly for the first 4 weeks and then once a month for the next 5 months of the study (i.e., nine lumbar punctures during the first 6 months of the study). The dose to each recipient was $1 \times 10^6$ interferon reference units at each treatment, except that at one centre patients received two half-dose treatments in the first week and then $1 \times 10^6$ interferon reference units at all the other treatments (i.e., ten lumbar punctures during the first 6 months of the study). Cerebrospinal fluid (CSF) was withdrawn for analysis before the injection of IFN-B at each lumbar puncture. Recipients also underwent a lumbar puncture after 2 years on the study so that CSF could be obtained for analysis. Control patients underwent placebo treatments according to the same schedule as the recipients. However, true lumbar punctures were carried out only at the beginning, after 6 months, and after 2 years on the study to obtain CSF for analysis; the remainder were false lumbar punctures in which the routine procedure (e.g., positioning, draping, skin cleansing, local anaesthetic) was followed but the needle was advanced only into the subcutaneous tissues, where 5 ml sterile water was injected. Recipients took indomethacin 25–50 mg every 6 h for 24 h after each treatment; controls took indomethacin (same dose) or placebo capsules according to the same schedule. Indomethacin, so administered, is known to reduce the side-effects of intrathecal interferon, which helped blinding of the patients.19

Treatments were carried out by a “treating” physician in an outpatient treatment room at each centre; afterwards the patient’s vital signs were monitored. The initial and subsequent examinations, assessing exacerbations and clinical status, were carried out by a separate “examining” physician at each centre who was not aware what treatment the patient had received. Patients did not discuss side-effects of treatments with the examining physician. Questionnaires completed by the patients and examining physicians during the study confirmed that both groups were blinded. A chi-square statistic based on a $3 \times 2$ table, testing the independence of each individual’s impression (IFN-B, placebo, unknown) from the routine procedure (eg, positioning, draping, skin cleansing, local anaesthetic) was followed by the numbers of patients whose impression could not be confirmed statistically.18

Results

The figure shows the exacerbation rates before and during the study for the two groups of patients. The exacerbation rates of both groups fell during the study: recipients mean 1.79 (SEM 0.17) to 0.76 (0.15) per year; controls 1.98 (0.21) to 1.48 (0.17) per year. However, the change was significantly greater in the recipients than in the controls ($102.6 = 0.51$ exacerbations per year: $p < 0.04$). The greater reduction in rate in recipients compared with controls was consistently observed at all three centres. The mean prestudy rates of the recipients and controls were nearly identical, but the recipients’ mean rate during the study was significantly lower than that of the controls

![Graph](image-url)
Discussion

It is known that the exacerbation rates of MS patients may fall over time as a natural phenomenon. However, studies of the changes in exacerbation rates of 393 MS patients26 show that, when our patients entered the study (illness duration 5-4 years in recipients, 6-1 years in controls) no decrease in rate in the study was expected. We therefore attribute most of the 57% reduction in exacerbation rate in recipients to the IFN-B treatment. We also attribute the uncoupling of dependence of the rate during the study on the prestudy rate observed in recipients (but not controls) to IFN-B treatment. The 26% reduction in exacerbation rate observed in the controls during the study might have been due to a placebo effect.

How intrathecal IFN-B might have had a beneficial effect in these patients is unknown; the mechanisms of interferon's actions are complex and incompletely understood. Interferon is a mediator of T-lymphocyte suppression; the treatment may have stabilised the fluctuations in suppressor T-cell activity known to occur during the course of MS, which have been postulated to be an integral part of the exacerbation/remission cycle.27-31 Alternatively, IFN-B may have changed the viral trigger for repeated exacerbations through clearance of a persistent CNS viral infection, possibly by inducing HL-A marker expression on the surface of infected cells, thus exposing them to the immune system.32-34 Such clearance could result in a transient increase in immunopathology and clinical exacerbation in some cases35-37 however, we could not statistically document an increase in exacerbations in our recipients during the treatment phase. IFN injected intrathecally does not pool in the lumbar sac, but flows upward over the surface of the cerebral convexities and comes into direct contact with brain parenchyma.38-39 While the mechanisms of its actions remain unknown, three studies have clearly shown that IFN-B acts in a prophylactic and suppressant way on the expression of experimental allergic encephalomyelitis, an animal model of MS.40-42 The IFN-B was most effective at the lowest doses when it was upregulated over the surface of the cerebral convexities and entered recipients directly into the CNS.

We will continue our follow-up of the patients in this study. In our preliminary study the IFN-B prophylactic effect against exacerbations persisted for 4-4-5-3 years in recipients. In our preliminary study the IFN-B prophylactic effect against exacerbations persisted for 4-4-5-3 years in recipients. It is clear that the study was not adequately powered to detect differences in exacerbation rates in the study. In conclusion, this study has clearly shown that IFN-B acts in a prophylactic and suppressant way in the treatment of multiple sclerosis patients treated with gamma interferon. Arch Neurol 1985; 42: 841-47.弓形虫</ref>