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MULTICENTRE DOUBLE-BLIND STUDY OF EFFECT OF INTRATHECALLY ADMINISTERED NATURAL HUMAN FIBROBLAST INTERFERON ON EXACERBATIONS OF MULTIPLE SCLEROSIS*

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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.[20-23] 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 criteria[23]) 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.[22,24] The prestudy exacerbation rate was determined by dividing the total number of exacerbations (standard definition[20-23]) 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, prestudy 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.[21]

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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,[1,2] 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.[19]

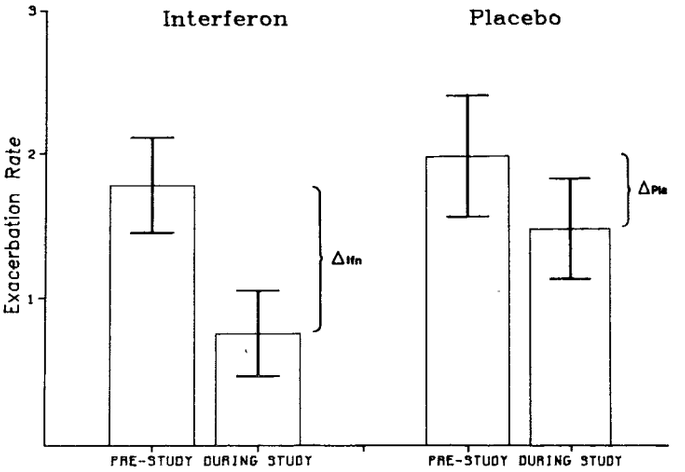
The IFN-B used was produced by superinduction of human fibroblast cells at Roswell Park Memorial Institute, Buffalo.[1,2] The preparation had a specific activity of 1×10^7 interferon reference units of IFN-B per mg protein. It was the same type as that used in the preliminary study and had passed the 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 (ie, nine lumbar punctures during the first 6 months of the study). The dose to each recipient was 1×10^6 interferon reference units at each treatment, except that at one centre patients received two half-dose treatments in the first week and then 1×10^6 interferon reference units at all the other treatments (ie, 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 (eg, 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.[25]

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 3×2 table, testing the independence of each individual's impression (IFN-B, placebo, unknown) from actual therapy received yielded an examining physician $p = 0{\cdot}66$ and a patient's $p = 0{\cdot}07$. The questionnaires also revealed that most patients who had an opinion believed they were receiving IFN-B (79·3% of recipients, 63·6% of controls).

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 (1·02 v 0·51 exacerbations per year: $p < 0{\cdot}04$). 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



Mean exacerbation rates (exacerbations/year) before and during the study in 34 recipients and 35 controls with MS.

Vertical bars represent 2SEM; △Ifn is reduction in recipient rates and △Pla reduction in placebo controls during study.

($p < 0{\cdot}001$). Correlation analysis revealed that the exacerbation rate during the study was strongly dependent on and directly proportional to the prestudy rate in the controls ($r = 0{\cdot}51$, $p < 0{\cdot}001$), but not in the recipients ($r = 0{\cdot}02$, $p = 0{\cdot}45$).

Clinically, 26 recipients (76·5%) and 21 controls (60%) were improved or unchanged, and 8 recipients (23·5%) and 14 controls (40%) were worse at the end of the study. The extent of deterioration was greatest in the controls (mean modified Kurtzke score increases: controls 0·80, recipients 0·32). However, this trend (recipients clinically stable or better; controls clinically worse) was not statistically significant (chi-square $p = 0{\cdot}23$).

Side-effects of treatment (headache, nausea, myalgia, lethargy) occurred with comparable frequency in recipients and controls, which may be attributed, at least partly, to the efficacy of indomethacin in reducing IFN-B side-effects. Low-grade fevers (mean 38·2°C) occurred more often in recipients (75%) than in controls (31%) (chi-square $p < 0{\cdot}001$), but this did not break the double-blinding (see above).

Pleocytosis and rises in CSF protein occurred in recipients during treatment. The maximum pleocytosis (mean $1{\cdot}22 \times 10^8$/l, range $0{\cdot}12$–$5{\cdot}66 \times 10^8$/l) and rise in protein (mean 590 mg/l, range 240–1600 mg/l) were noted during the first 5 weeks of treatment. At the last treatment (6 months), mean pleocytosis was $0{\cdot}25 \times 10^8$/l (range $0{\cdot}02$–$1{\cdot}88 \times 10^8$/l) and mean CSF protein 460 mg/l (range 150–1600 mg/l). At 2 years, mean pleocytosis was $0{\cdot}16 \times 10^8$/l (range $0{\cdot}01$–$0{\cdot}61 \times 10^8$/l) and the mean CSF protein was 460 mg/l (range 150–1600 mg/l).

2 of the recipients (5·5%) did not receive complete treatment courses because exacerbations developed within 1–30 days of IFN-B injections on two occasions, but both remained in the study and were followed for 2 years. The other 32 recipients (94·5%) tolerated the treatment regimen as scheduled, experiencing only the side-effects indicated above. 1 control patient died with rapidly progressive MS after 22 months on the study; she was included in the final analysis. Treating physicians at all three centres had the impression that exacerbations were being induced by IFN-B administration during the first 2 months of treatment in some patients with advanced disease, but this impression could not be confirmed statistically.

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 patients[26] show that, when our patients entered the study (illness duration 5·4 years in recipients, 6·1 years in controls) no decrease in rate would have been expected in either group during the study as a natural phenomenon. Therefore, we 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.[8,27-31] Alternatively, IFN-B may have changed the viral trigger for repeated exacerbations through clearance of a persistent CNS viral infection, possibly by inducing HLA-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 cases;[35-37] 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 administered directly into the CSF.[42]

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 without retreatment.[43-45] We emphasise that our treatment schedule may not be the optimum one. In the preliminary study, patients underwent thirteen treatments in 6 months; the number was reduced to nine in this study, and both regimens significantly reduced exacerbation rates. It is possible that even fewer treatments at different intervals might provide similar degrees of prophylaxis.

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