A multicentre, randomised, double blind, placebo controlled phase II study of subcutaneous interferon beta-1a in the treatment of patients with active rheumatoid arthritis


Published in:
Annals of the Rheumatic Diseases

Citation for published version (APA):

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A multicentre, randomised, double blind, placebo controlled phase II study of subcutaneous interferon beta-1a in the treatment of patients with active rheumatoid arthritis


Ann Rheum Dis 2005;64:64-69; originally published online 8 Jul 2004; doi:10.1136/ard.2003.020347

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EXTENDED REPORT

A multicentre, randomised, double blind, placebo controlled phase II study of subcutaneous interferon beta-1a in the treatment of patients with active rheumatoid arthritis


Objective: To assess the efficacy of interferon beta (IFNβ) in combination with methotrexate in treatment of patients with rheumatoid arthritis.

Methods: 209 patients with active rheumatoid arthritis, who had been on methotrexate for at least six months and at a stable dose for four weeks before study entry, were randomised in double blind fashion to receive placebo (0.05 ml or 0.5 ml), IFNβ 2.2 µg (0.05 ml), or IFNβ 44 µg (0.5 ml), given subcutaneously three times weekly for 24 weeks. The primary efficacy measure was a change in radiological scores at week 24. The secondary endpoint was the proportion of patients who met the ACR 20% improvement criteria at the end of the study. Synovial biopsy specimens were obtained before and after treatment from a subset of patients. Immunohistochemistry was used to detect the presence of inflammatory cells and the results were measured by digital image analysis. Collagen crosslinks were measured in urine at different times throughout the study.

Results: Analysis of radiological scores and clinical variable showed no changes in any of the groups, and there were no differences between the groups. On microscopic analysis of synovial tissue there was no significant change in the scores for infiltration by inflammatory cells after IFNβ treatment. Urinary levels of collagen crosslinks were unchanged between the treatment groups.

Conclusions: At the doses tested, treatment with IFNβ three times weekly in combination with methotrexate did not have a clinical or radiological effect in patients with rheumatoid arthritis.

Rheumatoid arthritis is a chronic inflammatory disease affecting synovial tissue in multiple joints, leading in most patients to bone destruction and severe morbidity and disability. Studies have shown the need for early diagnosis and early aggressive treatment to help prevent irreversible joint damage.1–3 The prevention of cartilage and bone destruction and severe morbidity and disability. Studies have shown the need for early diagnosis and early aggressive treatment to help prevent irreversible joint damage.4–6 Several studies in animal models of collagen induced arthritis (CIA) have shown a markedly beneficial effect of IFNβ treatment. A small study done in four rhesus monkeys with CIA demonstrated clinical improvement and decreased serum levels of C reactive protein after seven days of daily IFNβ treatment.7 Furthermore, constitutive expression of IFNβ by gene therapy resulted in reduced paw swelling and histological improvement in CIA mice.8 and CIA mice treated with daily injections of murine IFNβ had a significant reduction in inflammation and an inhibition of the development of bone erosions.9

The favourable effects on CIA in animal models and the well known safety profile of IFNβ treatment in humans motivated us to conduct an open label phase I study in 12 patients with active rheumatoid arthritis.10 Patients were treated with IFNβ subcutaneously three times weekly for three months with one of three different doses of fibroblast derived natural IFNβ (22 µg, 44 µg, and 66 µg) (Frote®, Serono International). The treatment was generally well tolerated and there was, on average, a significant improvement in clinical outcome measurements.

We undertook the present double blind, randomised, placebo controlled phase II study of treatment with IFNβ-1a (Serono International) in rheumatoid patients with active...
disease while on methotrexate to determine whether IFNβ-1a is effective in reducing radiological damage and arthritis activity.

**METHODS**

**Patients**

Patients over 18 years of age with a diagnosis of rheumatoid arthritis according to the American College of Rheumatology (ACR) criteria were eligible for inclusion in the study if the duration of their active disease was more than six months and less than eight years. Patients were also required to have at least eight swollen joints, and to fulfill no less than three of the following criteria: at least eight tender joints; physician’s global assessment of disease activity between 2 and 4 on a five point scale; patient’s global assessment of disease activity between 2 and 4 on a five point scale; serum C reactive protein above 15 mg/dl.

Patients were required to have used methotrexate for six months or more, and to have followed a stable regimen (≥7.5 mg/week) for at least four weeks before study entry. Patients who were on oral corticosteroids (<10 mg/day) or non-steroidal anti-inflammatory drugs (NSAIDs) were required to have been on a stable dose for at least four weeks before enrolment. Patients were required to have adequate bone marrow reserve, liver function, and renal function (haemoglobin ≥5.5 mmol/l, white blood cell count ≥3.5×10⁹/l, platelet count ≥100×10⁹/l; serum bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≤1.5 times the upper limit of normal values, and serum creatinine ≤150 μmol/l).

Women who were pregnant or lactating were excluded from the study, as were patients who had received biological agents or ciclosporin within the previous six months, had used a DMARD other than methotrexate within 28 days, or had used leflunomide within eight weeks of enrolment. All study participants were hospital outpatients at time of enrolment but were excluded if they were wheelchair bound or had a history of cancer in the preceding five years, or had a positive test for anti-dsDNA antibodies. Patients were excluded if clinically significant serious abnormalities were apparent on electrocardiography or chest x-ray; if they had had an active severe infection or an opportunistic infection in the three months preceding study entry; had a history of allergy to paracetamol or human serum albumin; or had a history of alcohol abuse.

**Study protocol**

Patients were randomised to one of four treatment groups: 2.2 μg (0.05 ml) IFNβ-1a, 44 μg (0.5 ml) IFNβ-1a, placebo (0.05 ml), or placebo (0.5 ml). All treatments were given by subcutaneous injection three times weekly for 24 weeks. Patients remained on a stable dose of methotrexate. Both the patients and the assessors were blinded to the treatment given. As IFNβ side effects are easily recognised, physicians responsible for general patient management, including safety assessments, were different from those responsible for efficacy assessments. Patients gave written informed consent before entering the study and the study protocol was approved by the local medical ethics committee at each of the participating sites.

**Safety and efficacy analyses**

The primary efficacy measure was defined as the change from baseline radiological score at 24 weeks of treatment, based on the presumed mechanism of action of IFNβ on osteoclasts and in line with previous observations showing that even modestly effective treatments may have a demonstrable protective effect on radiological joint damage after only 24 weeks of treatment. Anteroposterior radiographs of the hands and feet were scored using the Van der Heijde modified Sharp score by two independent blinded observers. Erosions in the feet were scored from 1 to 10, erosions in hands were scored from 1 to 5, and joint space narrowing was scored from 1 to 4. Scores were combined from hand and foot radiographs to provide a total score ranging from 0 to 448, with joint space narrowing scores ranging from 0 to 168 and erosion scores ranging from 0 to 280, with a maximum of 160 for the hands and 120 for the feet. The change in Van der Heijde x ray scores was calculated by the differences between the scores at the end of treatment and the scores on the baseline radiographs.

Secondary efficacy end points were defined as a 20% improvement in the ACR criteria (ACR20) and a decrease in C reactive protein concentrations. Clinical assessment for disease activity was repeated at baseline, day 15, day 29, and then every four weeks until week 28. This included a 68 joint count for joint swelling and tenderness; physician’s and patient’s assessment of disease activity on a scale from 0 (asymptomatic) to 5 (severe symptoms); assessment of pain by visual analogue scale from 0 (no pain) to 10 (severe pain); quality of life (health assessment questionnaire) from 1 (no disability) to 3 (severe disability); and erythrocyte

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**Table 1** Patient demographics, clinical characteristics, and previous treatment at baseline (ITT population)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Combined placebo group</th>
<th>IFNβ, 2.2 μg (n = 67)</th>
<th>IFNβ, 44 μg (n = 68)</th>
<th>All patients (n = 208)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.6 (11.7)</td>
<td>53.7 (12.8)</td>
<td>52.0 (11.1)</td>
<td>53.1 (11.9)</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>25.1 to 81.4</td>
<td>28.0 to 79.0</td>
<td>29.3 to 77.9</td>
<td>25.1 to 81.4</td>
</tr>
<tr>
<td>Female</td>
<td>65.8%</td>
<td>83.6%</td>
<td>83.8%</td>
<td>77.4%</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean duration (years)</td>
<td>4.1 (2.4)</td>
<td>4.2 (2.7)</td>
<td>4.2 (2.7)</td>
<td>4.2 (2.6)</td>
</tr>
<tr>
<td>Duration range (years)</td>
<td>0.6 to 9.5</td>
<td>0.6 to 12.5</td>
<td>0.5 to 10.4</td>
<td>0.5 to 12.5</td>
</tr>
<tr>
<td>Rheumatoid factor positive</td>
<td>71.2%</td>
<td>65.2%</td>
<td>65.2%</td>
<td>65.2%</td>
</tr>
<tr>
<td>Anti-CCP positive</td>
<td>54.8%</td>
<td>58.2%</td>
<td>55.9%</td>
<td>55.9%</td>
</tr>
<tr>
<td>Functional class I</td>
<td>15.1%</td>
<td>13.4%</td>
<td>17.6%</td>
<td>17.6%</td>
</tr>
<tr>
<td>Functional class II</td>
<td>67.5%</td>
<td>62.7%</td>
<td>72.1%</td>
<td>72.1%</td>
</tr>
<tr>
<td>Functional class III</td>
<td>24.7%</td>
<td>22.4%</td>
<td>10.3%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Functional class IV</td>
<td>2.7%</td>
<td>1.5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Concomitant MTX treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX dose (mg/week)</td>
<td>15.3 (4.6)</td>
<td>14.7 (5.5)</td>
<td>15.2 (5.1)</td>
<td>15.1 (5.0)</td>
</tr>
<tr>
<td>Length of MTX use (months)</td>
<td>19.0 (14.1)</td>
<td>16.4 (13.6)</td>
<td>17.1 (13.8)</td>
<td>17.6 (13.8)</td>
</tr>
</tbody>
</table>

Values are mean (SD) and range, or per cent.

CCP, cyclic citrullinated peptide; DMARD, disease modifying anti-rheumatic drug; ITT, intention to treat; MTX, methotrexate.
sedimentation rate (ESR) and C reactive protein measurement. In addition, rheumatoid factor, antibodies against cyclic citrullinated peptide (CCP), 22 and anti-IFNβ antibodies were measured by enzyme linked immunosorbent assay (ELISA) at screening, at week 12, and at week 24.

Safety assessments were completed at every visit by an independent observer, and included an interview, examination of vital signs, inspection of injection sites, and evaluation of current laboratory data. The use of concomitant drug treatment was recorded throughout the study.

Arthroscopy
Some patients underwent arthroscopy of an inflamed knee joint under local anaesthesia at baseline and at week 24. Patients gave separate written informed consent for this procedure. Arthroscopies, tissue sampling, and storage were carried out as described previously in detail. 23 All tissue samples were sent to the AMC, Amsterdam for immunohistochemical staining and digital image analysis.

Immunohistochemical analysis
Serial sections were stained with the following monoclonal antibodies (mAb): anti-CD68 (EBM11, Dako, Glostrup, Denmark), anti-CD55 (Clone-67, Serotec, Oxford, UK), and anti-CD3 (SK7, Becton-Dickinson, San Jose, California, USA). Sections with non-assessable tissue—defined by the absence of an intimal lining layer—were omitted before analysis. For control sections, the primary antibodies were omitted or irrelevant isotype matched mouse antibodies were applied. Staining was done according to a three step immunoperoxidase method as previously described. 24

Digital image analysis
The slides were evaluated by digital image analysis. All sections were coded and analysed in random order by an independent observer, who was blinded to the clinical data as described previously. 25

Urinary analysis of hydroxyypyridinium collagen crosslinks
The presence of the collagen hydroxyypyridinium crosslinks pyridinoline and deoxypyridinoline in urine is an indication of the breakdown of mature collagen. It has recently been shown that the total amount of pyridinium crosslinks excreted correlates with disease activity in rheumatoid arthritis. 26 The urinary excretion of pyridinoline (released primarily from collagens type I and II of bone and cartilage) and deoxypyridinoline (released primarily from collagens type I and II of bone and dentin) was measured at baseline, at week 12, and at week 24. Urinary crosslink levels were investigated using gradient ion-paired reversed phase high performance liquid chromatography. 26

<table>
<thead>
<tr>
<th>Events</th>
<th>Placebo, 0.05 ml (n = 34)</th>
<th>Placebo, 0.5 ml (n = 39)</th>
<th>IFNβ, 2.2 µg (n = 67)</th>
<th>IFNβ, 44 µg (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reaction</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>9 (13)</td>
<td>16 (24)</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>4 (12)</td>
<td>4 (10)</td>
<td>12 (18)</td>
<td>27 (40)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (12)</td>
<td>1 (3)</td>
<td>9 (13)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>1 (3)</td>
<td>4 (6)</td>
<td>10 (15)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (9)</td>
<td>1 (3)</td>
<td>4 (6)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5 (15)</td>
<td>4 (10)</td>
<td>11 (16)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Coughing</td>
<td>2 (6)</td>
<td>2 (5)</td>
<td>5 (7)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0</td>
<td>5 (13)</td>
<td>6 (9)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (12)</td>
<td>0</td>
<td>5 (7)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2 (6)</td>
<td>2 (5)</td>
<td>3 (5)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>SGPT increased</td>
<td>0</td>
<td>1 (3)</td>
<td>3 (5)</td>
<td>8 (12)</td>
</tr>
<tr>
<td>SGOT increased</td>
<td>0</td>
<td>1 (3)</td>
<td>2 (3)</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (9)</td>
<td>1 (3)</td>
<td>2 (3)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Rheumatoid arthritis aggravated</td>
<td>5 (15)</td>
<td>5 (13)</td>
<td>17 (23)</td>
<td>19 (28)</td>
</tr>
<tr>
<td>Increased ESR</td>
<td>2 (6)</td>
<td>3 (8)</td>
<td>6 (9)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Increased CRP</td>
<td>11 (32)</td>
<td>6 (15)</td>
<td>10 (15)</td>
<td>11 (16)</td>
</tr>
</tbody>
</table>

Values are n (%).

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IFNβ, interferon beta; SGOT, aspartate aminotransferase, SGPT, alanine aminotransferase.
**Statistical analysis**

The primary efficacy dataset was defined as all randomised patients for whom there were two sets of evaluable hand and foot x rays (one set for baseline and one set for week 24); patients who withdrew from study between week 12 and week 24 had x rays as soon as possible after the last injection of study drug) and who were not major protocol violators. The intention to treat (ITT) population comprised 208 patients who received at least one dose of study drug. For statistical analysis, the two placebo groups were combined and compared with the groups having IFNβ-1a treatment. The results before and after treatment were compared by paired t test. Two non-parametric tests were used: the Kruskal–Wallis test for several group means (comparing clinical assessment and histological scores in more than two treatment groups), followed by the Mann–Whitney U test for comparison of two groups. For the ACR20 response, non-completers of the study were considered to be non-responders.

**RESULTS**

**Patient characteristics and disposition**

In all, 209 patients were recruited from 30 centres in 10 countries during an eight month period. Their baseline characteristics are summarised in table 1. The mean (SD) age of the 161 women (77%) and 47 men (23%) was 53 (11.9) years. The median duration of disease was 3.6 years (range 0.5 to 12.5 years); 140 patients (67%) were rheumatoid arthritis; however, in the other groups no withdrawals were caused by injection site reactions. Flu-like symptoms, aggravated rheumatoid arthritis, and increased liver enzyme levels each caused the withdrawal of two patients from the other treatment groups: 10 patients in the IFNβ 44 µg group and four in the placebo groups. In the 44 µg group, injection site reactions caused the most adverse event related withdrawals (seven patients); however, in the other groups no withdrawals were caused by injection site reactions. Flu-like symptoms, aggravated rheumatoid arthritis, and increased liver enzyme levels each caused the withdrawal of two patients from the study population. Two patients tested positive for neutralising antibodies against IFNβ-1a at the end of treatment: both were receiving IFNβ 44 µg.

**Clinical efficacy**

There was no significant reduction in the progression of joint damage associated with treatment with IFNβ-1a at either of the doses tested compared with the control groups, as measured by the change from baseline in Van der Heijde x ray scores of the hands and feet (table 3). The 56 evaluable patients in the control group showed a median change of 1 (range –3 to 12), and the 37 evaluable patients in the 44 µg IFNβ group showed a median change of 0 (range –5 to 47). There were no statistically significant differences between the median ACR20 and ACR50 response rates between patients on active therapy and those in the control groups (fig 2).

**Immunohistochemical analysis**

Twenty five patients underwent synovial biopsy procedures, of whom 23 had results at baseline and 20 at the end of treatment (only 19 patients had both). The results of the immunohistochemical analysis are shown in table 4. After IFNβ 44 µg treatment there was a decrease in the number of

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Change from baseline in Van der Heijde x ray scores of the hands and feet before and after placebo or interferon beta treatment in patients with rheumatoid arthritis (evaluable population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline (%)</td>
<td>Placebo, 0.05 ml</td>
</tr>
<tr>
<td>Van der Heijde x ray score</td>
<td>1 (–12 to 17)</td>
</tr>
<tr>
<td>No of patients evaluable</td>
<td>56</td>
</tr>
</tbody>
</table>

Values are median (range).

IFNβ, interferon beta.

**Figure 2** American College of Rheumatology 20% (ACR20) response in the treatment groups (placebo groups combined).
CD68+ macrophages and a slight decrease in the number of intimal lining layer macrophages and CD3+ T cells, whereas CD55+ fibroblast-like synoviocytes increased slightly. None of these changes reached statistical significance. The IFNβ 2.2 µg treatment group showed a different trend, with an average increase in CD68+ intimal macrophages and CD55+ fibroblast-like synoviocytes and a slight decrease in CD3+ T cells; however, no statistically significant differences were detected when compared with placebo.

Collagen crosslinks analysis

There were no significant differences in urinary levels of the collagen crosslinks pyridinoline and deoxypyridinoline between patients treated with IFNβ and those treated with placebo. Levels of crosslinks were similar before treatment and after treatment in all groups. Thus median (range) pyridinoline concentrations, in nmol/nmol creatinine, were 17 (7 to 170) at baseline and 16 (5 to 88) at placebo; 75 (24 to 194) and 76 (30 to 212) with IFN 2.2 µg; and 75 (24 to 194) and 76 (30 to 212) with IFN 44 µg. Median (range) deoxypyridinoline concentrations, also in nmol/nmol creatinine, were 17 (7 to 170) at baseline and 16 (5 to 88) at week 24 with placebo; 19 (9 to 113) and 21 (9 to 38) with IFN 2.2 µg; and 18 (6 to 47) and 16 (9 to 65) with IFN 44 µg.

DISCUSSION

We report the results of a double blind, placebo controlled trial that evaluated the efficacy of subcutaneous IFNβ-1a on radiological and clinical variables in patients with rheumatoid arthritis who were concomitantly receiving methotrexate. Treatment with IFNβ-1a for 24 weeks was not associated with clinical or radiological improvement, neither was there a statistical change in biomarkers.

The absence of improvement in radiological scores after IFNβ treatment reported here is in clear contrast to previous work. Previous analyses of serial synovial tissue samples in patients with rheumatoid arthritis is likely to reflect the biological effects of the treatment given; for example, patients who received either placebo or unsuccessful treatment with recombinant human IL10 did not show any significant synovial changes.17 In contrast, beneficial clinical effects of anti-TNFα therapy are associated with decreased infiltration of synovial tissue by inflammatory cells.24 Consistent with this, our data show that persistent disease activity is associated with unchanged synovial inflammation in serial biopsy specimens in IFNβ treated rheumatoid patients. An earlier study suggested a modest reduction in CD3 positive T cells after one month of IFNβ treatment in synovial tissue of 11 rheumatoid patients. However, it was noted in the same study that the number of CD3 positive T cells returned to baseline levels after three months of treatment.

In conclusion, the results of this study show that there was no apparent reduction in the progression or activity of rheumatoid arthritis compared with placebo when methotrexate treatment was supplemented with IFNβ-1a in doses of either 44 µg or 2.2 µg over 24 weeks.

ACKNOWLEDGEMENTS

We are pleased to acknowledge the assistance and cooperation of our colleagues. We also thank the following investigators and their colleagues: B Bresnihan, Dublin, Ireland; H Dinant, Amsterdam, Netherlands; B Dijkstra, Amsterdam, Netherlands; P Emery, Leeds, UK; M Kraan, Amsterdam, Netherlands; R Inman, Toronto, Canada; C Jackson, Salt lake City, USA; J Kaltwasser, Frankfurt, Germany; E Keystone, Toronto, Canada; P Maddison, Bath, UK; W Maksymowycz, Edmonton, Canada; B hareou, Montreal, Canada; M Molloy, Madrid, Spain; B Kidd, London, UK; N Wei, Maryland, USA; M Molloy, Cork, Ireland; L Moreland, Birmingham, Alabama, USA; R Rau, Ratingen, Germany; R Rodriguez, Sevilla, Spain; D van Schaardenburg, Spain; B Kidd, London, UK; N Wei, Maryland, USA; M Molloy, Cork, Ireland; L Moreland, Birmingham, Alabama, USA; R Rau, Ratingen, Germany; R Rodriguez, Sevilla, Spain; D van Schaardenburg.
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