Recombinant human interferon γ in the treatment of rheumatoid arthritis: double blind placebo controlled study

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Abstract

Interferon gamma (IFN γ) has been advocated in open studies as a beneficial remission inducing drug for the treatment of rheumatoid arthritis (RA). The work reported here was designed to assess the therapeutic potential of IFN γ in the treatment of RA in a double blind placebo controlled study. It was found that patients treated with IFN γ improved significantly with respect to morning stiffness, grip strength, swelling of an index joint, and erythrocyte sedimentation rate. Furthermore significantly more responders (according to predetermined response criteria) were found in the group treated with IFN γ . Only minor adverse effects and no significant toxicity with respect to clinical or laboratory parameters were observed.

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Rheumatoid arthritis (RA) is the most common inflammatory rheumatic disease leading to joint destruction and to longstanding crippling disease. Treatment consists currently of symptomatic drugs in combination with the so called disease modifying drugs.¹ The latter, such as gold salts, D-penicillamine, hydroxychloroquine, sulphasalazine, and cytostatic drugs, have limited efficacy and significant toxicity.¹⁻⁸ Therefore as long as the aetiology of the disease and thus effective treatment is unknown, new disease modifying drugs with similar or better efficacy and lesser toxicity than presently available are required.

As RA is an immune mediated disease⁹⁻¹¹ beneficial effects might be expected from modulation of the immune response. Naturally occurring biological response modifiers such as the interferons have attracted attention as therapeutic drugs.¹² With respect to RA reports of open studies of treatment with interferon γ (IFN γ) have indicated beneficial effects.^{13 14}

In this work we analysed the potential efficacy of IFN γ in the treatment of patients with RA in a double blind placebo controlled study.

Patients and methods

STUDY DESIGN

The study was designed as an eight month double blind study of IFN γ versus placebo with a crossover after four months and was approved by the ethical committee of the University of Vienna. Patients gave informed consent after the study design had been discussed extensively with them. In particular patients

were informed of potential side effects of IFN γ such as fever, flu-like symptoms, leucopenia, and thrombocytopenia.

PATIENTS

Thirty three patients with classical or definite rheumatoid arthritis according to the 1958 American Rheumatism Association (ARA) criteria¹⁵ entered the study. Table 1 gives the inclusion criteria. Inefficacy (after at least six months of treatment) or intolerability of previous treatment with at least one of the established disease modifying drugs (in particular gold salts, hydroxychloroquine, or D-penicillamine) was mandatory. None of the patients had received disease modifying drugs for at least four weeks before inclusion in the study. At inclusion patients were randomised according to age, sex, and disease activity. Table 2 gives the patients' status at randomisation.

All patients had exacerbations of their disease at the time of inclusion and were admitted as inpatients for two weeks. Thereafter they were regularly monitored on an outpatient basis.

DRUG TREATMENT

Recombinant human IFN γ (code IF-RC 1001 XX G) was obtained from Genentech (South San Francisco, CA, USA) through Bender and Co (Vienna, Austria). One vial contained 0.5

Table 1 Criteria for inclusion of patients to the study

- A Classical or definite rheumatoid arthritis according to the 1958 American Rheumatism Association criteria¹⁴
- B No response to at least one classical disease modifying drug such as gold salts, hydroxychloroquine, or D-penicillamine
- C Cessation of treatment with disease modifying drugs because of inefficacy or side effects at least four weeks before inclusion in the study
- D Erythrocyte sedimentation rate >30 mm/hour
- E Morning stiffness for at least one hour
- F Three or more joints swollen or painful, or both
- G Mean grip strength <200 mmHg

Criteria A-C were mandatory and in addition three of the four criteria D-G had to be present.

Table 2 Status of patients at inclusion in the study

	Group A (IFN γ - placebo)	Group B (placebo- IFN γ)
Sex (F/M)	13/4	12/4
Disease stage (Steinbrocker)		
Stage II	13	13
Stage III	4	3
Previous treatment		
Gold salts	15	13
D-Penicillamine	9	6
Hydroxychloroquine	9	10
Steroids	6	6

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mg IFN γ with a specific activity of 2×10^7 IU/mg protein as a lyophilised powder. The powder was resuspended before application in 1 ml distilled water and was used immediately; 0.2 ml of the reconstituted solution was injected subcutaneously three times a week (dose in each injection 100 μ g). The placebo contained all the ingredients except for IFN γ and was indistinguishable in appearance from IFN γ .

All patients were allowed to use non-steroidal anti-inflammatory drugs (NSAIDs) (diclofenac, indomethacin, or ibuprofen).

CLINICAL EXAMINATION AND LABORATORY TESTING

Clinical examinations were always performed blindly by the same doctor. For evaluation of clinical efficiency the following parameters were assessed: morning stiffness, grip strength, circumference and swelling of an 'index joint', indices for joint pain and swelling, and the patient's and doctor's assessment of severity of illness.

The duration of morning stiffness was recorded at every examination and graded into four groups for randomisation and statistical evaluation (<30, 30–60, 60–120, and ≥ 120 min).

Grip strength was measured by a sphygmomanometer connected to a soft rubber cuff (vigorimeter) and the mean value of three consecutive measurements (in mmHg) was recorded.

Swelling of index joints was measured by a set of jeweller's rings for proximal interphalangeal joints and a tape measure around the maximum circumference of wrist or knee joints.

Tenderness of joints was examined according to Ritchie *et al.*,¹⁶ by testing 48 diarthrodial joints for pain on firm pressure grading from 0=none to 3=severe; joint regions such as metacarpophalangeal or metatarsophalangeal joints were included in the index as one value.

'Severity of illness' was estimated by the patient and the doctor by grading from 0=none to 3=severe.

Each patient kept a daily diary in which the duration of morning stiffness, intensity of pain, and intake of NSAIDs were recorded. At each clinical examination patients were also asked about the occurrence of potential side effects or unexpected symptoms.

LABORATORY ANALYSES

Blood samples were taken for the determination of blood chemistry (American Parallel 20 analyser), blood counts, electrophoresis, Westergren erythrocyte sedimentation rate, fibrinogen, ferritin, rheumatoid factor, anti-nuclear antibodies, immunoglobulin and complement levels.

The study was planned as a crossover investigation with a change of treatment after the first four months. Examinations were performed at the end of weeks 1, 2, 3, and 4, and months 2, 3, and 4; in addition patients were to be re-evaluated one month after the end of the eight month treatment period.

EVALUATION AND STATISTICAL ANALYSES

To assess the overall efficacy of treatment the individual parameters were compared between the two groups (IFN γ *v* placebo) and within each group (values before *v* end of treatment period). In addition as complete remission according to the ARA criteria¹⁷ was not necessarily expected, an arbitrary set of response criteria (table 3) was defined and the number of patients receiving IFN γ and placebo fulfilling these criteria were compared.

Comparisons between groups were made using the Wilcoxon and Mann-Whitney U tests for continuous data and contingency tables for categorical data; intragroup comparisons were carried out using the Wilcoxon signed rank test and the sign test. Of the 33 patients who had entered the study 31 were evaluable after the first four month period. Seventeen patients had received IFN γ and 16 placebo; two patients (one in each group) had withdrawn their approval.

For the second four month period—that is, after crossover—only 14 patients remained. Their clinical data were not used for statistical analyses; however, results of this second period will be discussed despite the limitations of interpreting data from such low numbers of patients.

Results

FIRST PERIOD

Morning stiffness

Figure 1 shows the assessment of morning stiffness in the two treatment groups. At the end of the observation period significantly more patients (13 patients) had morning stiffness for less than 60 minutes compared with the number of patients with morning stiffness for less than 60 minutes before the beginning of treatment with IFN γ (two patients, $p < 0.001$) and with the number of patients with morning stiffness less than 60 minutes at the end of placebo treatment (eight patients, $p < 0.05$). Within the placebo group the number of patients with morning stiffness for less than 60 minutes did not differ significantly when the beginning and end of the treatment period were compared.

Grip strength

In patients receiving IFN γ there was a significant increase of grip strength in the right hand (mean (SEM) 94 (10.9) mmHg *v* 120 (15.3) mmHg, $p < 0.05$), and a similar trend of grip strength in the left hand (95 (10.6) mmHg *v* 115 (16.2) mmHg, $0.05 < p < 0.1$). In contrast such a trend was not seen in the placebo group.

Table 3 Clinical response criteria

Morning stiffness <30 minute
Increase of grip strength by $\geq 50\%$ compared with initial value
Severity of disease assessed by the patient as 1 (=mild) or less
Improvement of the Ritchie index by more than 25% compared with the initial value

Clinical response was judged by the presence of at least three of these criteria on at least three of the monthly follow up examinations.

Swelling of index joint

A single joint with marked synovitis was chosen before treatment as an 'index joint'. Swelling was measured around its maximum circumference. To account for differences between small and large joints pretreatment measures were regarded as 100% and later measurements expressed in percentages related to these initial values. Figure 2 shows that the group treated with IFN γ had a decrease in index joint circumference ($p < 0.01$, Wilcoxon signed rank test). Patients receiving placebo did not have such an improvement.

Figure 1 Morning stiffness before and during treatment. At the end of the first four months of treatment improvement was seen in the IFN γ group ($p < 0.001$, sign test) but not in the placebo group; the difference between the two treatment groups was significant ($p < 0.05$).

Figure 2 Swelling of index joint. Swelling of a predetermined 'index joint' decreased significantly in the IFN γ group ($p < 0.01$) but not in the placebo group (Wilcoxon signed rank test).

Ritchie index

Although indices improved to a larger degree in the group treated with IFN γ compared with the placebo group the differences seen did not reach statistical significance (mean IFN γ : before 17 (SEM 2.2), after 15 (2.0); placebo: before 20 (1.5), after 21 (3.1)).

Clinical response

To obtain a more general estimate of the potential beneficial effects of IFN γ in addition to comparing individual parameters, a number of arbitrary response criteria were determined (see table 3). Eight of 16 patients evaluated in the group treated with IFN γ but only two of the 15 patients treated with placebo fulfilled these criteria ($p < 0.05$).

Laboratory parameters

In the group treated with IFN γ the mean erythrocyte sedimentation rate decreased from 74 (SEM 7.7) to 60 (8.8) mm/hour ($p < 0.05$; placebo 78 (9.8) to 69 (7.7) mm/hour, not significant). In addition ferritin levels decreased from 158 (52.4) to 111 (38.2) ng/ml ($p < 0.05$) in the group treated with IFN γ (placebo 92 (39.9) v 105 (49.9) ng/ml, not significant).

Other laboratory parameters recorded did not show significant changes. In particular there was no evidence for adverse effects on hepatic, renal, or bone marrow function.

Side effects

The most common side effect was fever which occurred in 14 of 16 patients in the group treated with IFN γ , but also in five of the 15 patients in the placebo group. The range of fever was 37.5–39°C. In one patient receiving IFN γ the dose was reduced to 50 μ g (50% of the initial dose) in each injection from weeks 3 to 7 because of this side effect. Fever did not recur when the original dose was resumed. Other concomitant events reported were chills (IFN γ 10/16, placebo 3/15), fatigue (IFN γ 7/16, placebo 3/15), loss of appetite (IFN γ 3/16, placebo 2/15), myalgia (IFN γ 3/16, placebo 0/15), vertigo, headache, night sweats, and itching (less than three patients overall).

Withdrawals

Two patients (one in each group) withdrew their consent because of severe exacerbation of their disease within the first two weeks of the study and have not been included in the statistical evaluation. One patient in the IFN γ group refused to complete treatment after three months because of lack of efficacy; nevertheless she has been included into the initial evaluation, but did not enter the second period of study.

SECOND PERIOD

Data evaluation

Owing to the high number of patients who did not wish to continue or complete the trial, this phase of the trial was not evaluated statistically.

We feel, however, that the observations of this second period deserve description and will focus mainly on the clinical outcome of the patients in the two groups and on the reasons for discontinuation of treatment.

Withdrawals

At the end of the first period each treatment group consisted of 15 patients. Two patients of the original group treated with IFN γ (group A) and three of the original placebo group (group B) refused to enter the second period; of these one in each group did not want to risk deterioration of his or her already improved condition; the others (one in group A and two in group B) had not felt that there was an improvement of their disease and therefore refused to continue their participation. Thus at the beginning of the second period group A consisted of 13 patients and group B of 12 patients.

Of the 13 group A patients (placebo in period 2) further withdrawals occurred as follows. At the end of month 1 one patient experienced a deterioration of her condition after having improved significantly during the first period and refused to continue the double blind study. At the end of month 2 two patients withdrew from the trial. One patient who had not had any detectable clinical changes in period 1 refused to continue treatment because of continuing lack of efficacy; the other patient who had improved in period 1 still felt well, but decided that she did not want to risk a deterioration of her improved condition. At the end of month 3 one patient, who had slightly deteriorated in period 1 and had not shown a change in her condition in period 2, did not attend her scheduled control examinations and had therefore to be excluded from the study. Thus only nine group A patients completed the study to the end of the crossover period.

Of the 12 group B patients (IFN γ in period 2) who entered the second period we noted the following withdrawals. At the end of week 1 one patient had to be treated with systemic corticosteroids because of an exacerbation of his pre-existing bronchial asthma and was withdrawn as required by the study protocol. His arthritic condition had improved significantly in the first period (this patient had been one of the two clinical responders in the placebo group). At the end of month 1 one patient decided to undergo reconstructive knee surgery and discontinued treatment. At the end of month 2 two patients who had not experienced any significant changes in their clinical status during period 1 withdrew. One of them improved dramatically after switching to IFN γ (improvement of the Ritchie index from 34 to 9), but did not keep her scheduled appointments; the other patient discontinued treatment because of lack of efficacy. At the end of month 3 three patients refused to continue treatment because of a lack of efficacy. Thus of the 12 group B patients five continued the study to the end of the crossover period.

Clinical changes

Of the nine group A patients (IFN γ switched to

placebo) whose data were available for evaluation for more than three months of the second period, five had experienced a clinical improvement during the first period. Their clinical condition during the second period showed neither further improvement nor deterioration, but the subjective impression of a persisting beneficial effect prevailed with both the patients and the examining doctor. The clinical data for the other four patients who had not been responders in the first period did not show any trends towards improvement or deterioration except for one patient who showed considerable clinical deterioration.

Among the five group B patients (placebo switched to IFN γ) who were observed for more than three months in the second period, one had been classified as a responder in the first period. In one patient who had deteriorated during the first period this negative trend continued throughout the second phase of the study. All other four patients (including the placebo responder) showed an improvement in their clinical parameters (data not shown).

The data from the second period are reported here for reasons of record and completeness only, as the low number of observations, due primarily to lack of compliance, does not allow reliable statistical analysis; however, as can be seen from our observations, the second period did not contradict the results of the first.

Discussion

In this study the efficacy of treatment of RA with IFN γ was evaluated in a double blind placebo controlled trial which had been originally designed as a crossover investigation. Despite the low number of patients entered into the protocol, significant improvement was noted in the group treated with IFN γ for the first period but not in the placebo group, with respect to morning stiffness, grip strength, index joint swelling, erythrocyte sedimentation rate, and ferritin levels. An arbitrary set of response criteria was fulfilled by 50% of the patients treated with IFN γ in the first period, but only by 13% of patients receiving placebo. Although these response criteria have not been validated in other studies they refer to parameters generally accepted as clinical indicators of disease activity, extending individual parameters analysed at each examination over a longer time period. These criteria had been defined before the initiation of the study and were thus equal for all patients. Each of the parameters 1 to 3 (table 3) is a strong indicator of severity of disease, probably more so than the Ritchie index.¹⁸

Despite these apparently beneficial effects it is difficult to assess the results of this study. The first period, although characterised by the reported improvements, showed that the Ritchie index did not improve significantly in the patients treated with IFN γ . This may, however, be due to the wide range of individual indices in a relatively low number of patients rather than to lack of efficacy, particularly as other parameters of disease activity improved significantly. It should also be noted that before inclusion in the study all patients had previously

been treated unsuccessfully with disease modifying drugs. This was included for ethical reasons, but may have led to a negative selection bias in the study.

The interpretation of the second period—that is, after crossing over from placebo to IFN γ and vice versa—is difficult for several reasons. First only 14 patients completed the second period, a number which did not allow reliable statistical comparisons. Although in the second period the withdrawals due to lack of efficacy in patients receiving IFN γ was higher than in those receiving placebo, this could reflect the longevity of inefficacious treatment in the first period.

Second, four of the five patients who completed period 2 while receiving IFN γ were responders. This response (33% of the patients entering period 2) is close to the percentage of responders in the first period (50%), particularly in view of the prolonged period of inefficient placebo treatment which had preceded this second phase of the trial.

In contrast, the number of responders receiving placebo in the second period cannot easily be evaluated as some patients had already seen an improvement in their condition while receiving IFN γ treatment and the natural history of such improvements is unknown. Eight of the nine patients who completed period 2 while receiving placebo had not deteriorated during this phase of the study compared with the evaluation at crossover; this could be interpreted as a potentially sustained beneficial effect of the treatment with IFN γ in the first period. This is further indicated by the sustained positive effects during the four week follow up period without any treatment in the 14 patients who had completed the whole course of the study.

The results obtained in this study indicate that IFN γ may be active as a disease modifying drug as it improves the clinical course of the disease, as improvement is gradual rather than prompt, and as the effect appears to last longer than the time for which the drug is given. In addition a mild but significant reduction in the erythrocyte sedimentation rate was noted, another characteristic of disease modifying drugs.

In contrast to other currently available disease modifying drugs no serious side effects were seen; the major side effect was a febrile reaction, which was also observed with the placebo. Retrospective analysis could not clarify whether this observation was due to the placebo preparation (which had been determined repeatedly to be free of pyrogens) or to some expectations of the patients on the basis of the information included in the informed consent sheet. IFN γ therefore appears to be a safe drug. This finding is in agreement with other investigations.

With regard to efficacy some workers have observed significant beneficial effects in open^{13 14} and in controlled¹⁹ studies; others^{20 21} have observed only mild beneficial effects of IFN γ . Differences in dose, application schedule, or duration of treatment may have accounted for these variations.

In conclusion we feel that further studies using IFN γ should now primarily concentrate on optimisation of schedules for the dose and frequency of application. It may also be of value to study IFN γ in combination with other drugs such as immunosuppressive drugs. In addition it may be important to determine criteria characteristic of patients with RA who are responsive to IFN γ .

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