Nonathymulin in rheumatoid arthritis: two double blind, placebo controlled trials

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SUMMARY Two randomised double blind, placebo controlled trials have been carried out to assess the effectiveness of nonathymulin, a synthetic thymic peptide hormone, in the treatment of rheumatoid arthritis (RA) and to compare three different dosage schedules (1, 5, and 10 mg/day). Nonathymulin 5 mg proved to be the most efficient dose, providing significant clinical improvement as evaluated by the global assessment of all patients who entered the trials (56% v 17% in the placebo group) ($p < 0.02$) and by four objective parameters. This effect was accompanied with minimal adverse effects and was not associated with clear changes in immunological parameters. A significant correlation was observed, however, in clinical response to nonathymulin, and T cell subset imbalance was assessed using monoclonal anti-T cell antibodies and a functional suppressor T cell assay.

Key words: thymic peptide hormone.

Several immunomodulating agents have been reported to improve the course of rheumatoid arthritis (RA). This has been particularly true in the case of two T cell stimulating agents, levamisole¹ and thymopentin.² We report here a clinical trial in RA of the thymic hormone, nonathymulin (formerly called FTS for Facteur Thymique Sérique), which, like thymopentin, is involved in intrathymic T cell differentiation.³

We previously reported the effects of nonathymulin in RA in two open trials using respectively 150 µg and 1 mg nonathymulin subcutaneously each day for two weeks and then three times a week for four months. A beneficial effect of nonathymulin on the course of the disease was observed at a dose of 1 mg.⁴ The present study includes two randomised double blind, placebo controlled trials that aim to assess the effectiveness of nonathymulin in the treatment of RA and to compare three different dosage schedules (1, 5, and 10 mg/day).

Patients and methods

PATIENTS

Patients with RA fulfilling the American Rheuma-

tism Association's criteria for definite or classic disease⁵ entered the studies after giving informed consent. Other criteria for entry were the presence of active disease defined by at least three of the following: erythrocyte sedimentation rate of 30 mm/h or higher, 60 minutes or more of morning stiffness, a Ritchie index⁶ of 10 or more, a Lee functional index⁷ of five or more, and at least three joints with effusion or synovitis. Corticosteroids and non-steroidal anti-inflammatory drugs or analgesics, or both, were maintained, and the drug dosages used by the patient during the trial were noted.

Patients with a serious concomitant medical illness judged to be in functional class IV by the criteria of the American Rheumatism Association⁸ or with a history of cancer, liver, or renal disease were excluded from the study. Patients were not accepted into the trial until slow acting antirheumatic drugs had been withdrawn for at least three months. During the study each patient remained under the care of the same investigator.

DESIGN OF STUDIES

Studies were double blind and of six months' duration. Patients and investigators remained unaware of drug assignments until each study was completed. Patients were randomly assigned to receive indistinguishable subcutaneous injections. In the first trial, injections of nonathymulin 1 mg

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(Thy 1), nonathymulin 5 mg (Thy 5), or placebo were given each day for the first two weeks and then three times a week. In the second trial, injections of nonathymulin 10 mg (Thy 10) or placebo were given each day for six months. In both trials the placebo contained zinc sulphate at the same concentration as in the nonathymulin preparation (nonathymulin is a synthetic metallopeptide containing zinc).^{3 9}

CLINICAL ASSESSMENTS

Each patient was examined by the same medical investigator every two months early in the morning. The clinical disease variables determined at each visit comprised (a) duration of morning stiffness, (b) grip strength (total in mmHg of three consecutive measurements on each side), (c) proximal interphalangeal circumference (total of 10 joints), (d) Ritchie index,⁶ (e) Lee functional index,⁷ (f) pain assessment (on 100 mm visual analogue scale), (g) two monthly assessment by patient of his or her own state compared with that at the previous examination (+3 = much better; +2 = better; +1 = slightly better; 0 = identical; -1 = slightly worse; -2 = worse; -3 = much worse), and (h) average of daily prednisone consumption in milligrams.

The overall assessment by the investigator and the patient at the end of the study was considered to be the main criterion. This overall assessment was evaluated on a scale of 0 = nil, 1 = mild, 2 = good, 3 = very good.

LABORATORY TESTS

Detailed blood counts including platelets count and the erythrocyte sedimentation rate were obtained every month. Serum creatinine and liver enzyme tests, including measurement of serum aspartate, alanine aminotransferase, alkaline phosphatase, and cholesterol, were measured every two months.

IMMUNOLOGICAL STUDIES

Immunological studies were performed at entry and on completion of the first trial.

Rheumatoid factor and antinuclear antibodies were studied according to conventional techniques.

Lymphocyte subsets were studied using the OKT series of monoclonal antibodies (OKT3 directed against all mature T cells, OKT4 directed against the helper/inducer subset, OKT8 directed against the suppressor/cytotoxic subset).¹⁰ The microscopic immunofluorescence technique used to evaluate the size of each T cell subset pool has already been described.¹¹

Suppressor activity of T lymphocytes on IgM production of B lymphocytes infected by Epstein-Barr virus (EBV) was performed as previously reported.¹² The response of the patients with RA in

this test was classified into two groups according to suppressive activity of the T lymphocytes: group 1 in which the decrease in IgM production in B+ autologous lymphocyte cultures was more than 50% versus IgM production observed with B cell culture alone (the pattern usually observed in normal subjects); group 2 in which IgM production in B+ autologous lymphocyte cultures did not differ or was higher than in B cell culture alone, suggesting the existence of a deficiency of T cell suppressor function.¹²

STATISTICAL ANALYSIS

Statistical analysis was performed to assess the significance of the effect of nonathymulin on the whole group of patients entering the trials and the effect on patients who continued treatment until completion of the study. Owing to the abnormal distributions of many of the response variables, statistical analysis was made by non-parametric tests. A p value of less than 0.05 was considered significant. Because of the small number of patients, included in these trials the 90% confidence interval for the difference in response between placebo and nonathymulin group patients have been evaluated.¹³ Additionally the relation between the clinical response and the immunological status at entry were studied by the χ^2 or Fisher's exact test.

Results

PATIENTS AND STUDY COURSE

In the first trial, of the 49 patients enrolled, 17 were initially assigned to receive placebo, 16 nonathymulin 1 mg, and 16 nonathymulin 5 mg. There were no significant differences at entry for demographic and RA variables among the three groups (Table 1), except for the immunological status of the patients. Normal T lymphocyte suppressor function was observed in 10 out of the 16 patients receiving nonathymulin 5 mg compared with only three out of the 16 receiving nonathymulin 1 mg, and four of the placebo group ($p < 0.025$). Five patients dropped out before the completion of the study. Two of these patients were receiving placebo; one was withdrawn after three days because of painful injections and the other because of inefficacy of treatment at month 4. One of the patients receiving nonathymulin 1 mg was withdrawn at month 4 because of treatment inefficacy. Two patients receiving nonathymulin 5 mg were withdrawn because of side effects; one developed peripheral thrombocytopenia at month 3 and the other showed vasculitis at month 5.

In the second trial, of the 30 patients enrolled, 15 were initially assigned to receive placebo and 15 to nonathymulin 10 mg. At entry there were no

Table 1 Demographic and RA variables at study entry by treatment group in the two trials: mean values (standard deviation)

Variable	First trial			Second trial	
	Placebo (n=17)	Thy 1 mg (n=16)	Thy 5 mg (n=16)	Placebo (n=15)	Thy 10 mg (n=15)
Age (years)	53 (9)	57 (12)	59 (11)	51 (11)	57 (10)
Male/female	1/16	2/14	3/13	3/12	1/14
Mean disease duration (years)	13.0 (6.8)	12.8 (8.8)	13.6 (7.1)	11.5 (7.4)	13.5 (8.2)
Rheumatoid factor positive	15	14	13	13	12
Morning stiffness (min)	132 (105)	140 (125)	120 (105)	121 (137)	197 (132)
Grip strength (mmHg)	300 (218)	286 (322)	335 (30)	263 (308)	227 (259)
PIP [†] joint circumference (mm)	510 (44)	568 (47)	598 (80)	572 (44)	557 (39)
Lee index	12 (6)	11 (4)	12 (5)	12 (6)	13 (5)
Ritchie index	19 (8)	16 (9)	18 (5)	18 ( )	16 (7)
Pain (on 100 mm visual analogue scale)	65 (26)	65 (25)	63 (23)	64 (30)	63 (19)
Swollen joints (number)	16 (7)	12 (6)	15 (6)	11 (5)	10 (6)
Prednisone consumption (mg/day)	6 (5)	6 (5)	6 (6)	7 (4)*	10 (4)
T lymphocyte suppressive effect	11/15**	13/16**	6/16	ND‡	ND‡

* $p < 0.01$ (significance determined by the Mann-Whitney U test); ** $\chi^2 = 7.46$, $p < 0.025$.

†PIP = proximal interphalangeal.

‡ND = not determined.

significant differences of demographic and RA variables between the two groups except for corticosteroid daily consumption, which was higher in the nonathymulin 10 mg group than in the placebo group ($p < 0.01$) (see Table 1). Six patients withdrew before completion of the study: three in the placebo group (inefficacy at month 4) and three in the nonathymulin 10 mg group (adverse reaction at day 1 (one patient) and at month 1 (one patient); inefficacy at month 2 (one patient)).

All patients withdrawing from the studies were included in the global assessment analysis as a treatment failure (0 = nil), but they were excluded from the analysis of other clinical disease variables.

RESPONSE TO TREATMENT: GLOBAL ANALYSIS OF ALL PATIENTS WHO ENTERED THE TRIALS

The patient's expectation of benefit, i.e., personal assessment of response to treatment, was first considered in all patients who entered the first trial. The three groups differed significantly ($p < 0.02$); moderate or major improvement was observed in 17.6% of patients receiving placebo compared with 62.5% of patients receiving nonathymulin 5 mg. The clinical improvement appeared to be better in patients receiving the higher nonathymulin dosage since a good or very good effect was observed in 37.5% of patients receiving nonathymulin 5 mg compared with only 12.5% of patients receiving nonathymulin 1 mg. Data in Table 2 show that the

approximate 90% confidence interval for the difference in true response probabilities between placebo and nonathymulin 1 mg group patients is 13.2% to 64.1%, in all cases favouring nonathymulin. This 90% confidence interval is 19.9% to 69.9% when comparing placebo and nonathymulin 5 mg group patients, also favouring nonathymulin in all cases. In the second trial similar improvement was observed in patients receiving nonathymulin (moderate or major improvement in 53.3% and major improvement in 26.6%), but this was not significantly different from the result for the placebo group, in which there was also some improvement. It is, however, interesting to note that the approximate 90% confidence interval for the difference in true response probabilities between placebo and nonathymulin 10 mg group patients is -9% to 49%, i.e., from only 9% favouring placebo to 49% favouring nonathymulin 10 mg.

RESPONSE TO TREATMENT OF PATIENTS WHO COMPLETED SIX MONTHS OF THE TRIAL

In the first trial 44 patients remained in the trial to completion: 15 in the placebo group, 15 in the nonathymulin 1 mg group, and 14 in the nonathymulin 5 mg group. In the second trial 24 patients, 12 in each group, remained in the trial to completion. The differences between all groups were only significant for patient self assessment when using the Kruskal-Wallis test in the first trial and the Mann-Whitney U test in the second trial. In the first trial, however, a

Table 2 Overall assessment by the patient and the investigator by treatment group for all patients who entered the trials

Assessment	First trial			Second trial	
	Placebo	Thy 1 mg	Thy 5 mg	Placebo	Thy 10 mg
Nil	14	7	6	10	7
Moderate	1	7	4	4	4
Good	2	1	4	1	4
Very good	0	1	2	0	0

separate comparison of each treated group (1 and 5 mg) with the placebo group by the Mann-Whitney U test showed that patients receiving nonathymulin 1 mg were not significantly different from patients receiving placebo except for patient self assessment ($p<0.05$). At variance, patients receiving nonathymulin 5 mg did significantly better than patients given placebo for four clinical variables measured at the end of six months (Table 3). Grip strength increased from 335 to 392 in nonathymulin treated patients and decreased from 300 to 234 in placebo treated patients ($p<0.03$). Lee functional index improved in nonathymulin treated patients with a decrease from 12 to 9 and remained stable at 12 in placebo treated patients ($p<0.05$). Furthermore, in nonathymulin treated patients the prednisone consumption decreased significantly from 6 to 4.4 mg/day and remained stable in placebo treated patients ($p<0.05$). In the second trial a similar improvement was observed in patients receiving

nonathymulin 10 mg but without significant difference when compared with the placebo group. Interestingly, in both trials clinical improvement was not correlated with any biological changes (sedimentation rate, rheumatoid test, T lymphocyte subsets).

ADVERSE REACTIONS

In the first trial five patients were withdrawn from the study for various reasons already mentioned (treatment inefficacy (two patients), side effects (three)). Of the three patients withdrawn for an adverse drug reaction, two were taking nonathymulin 5 mg.

Asymptomatic thrombocytopenia (5×10^9 platelets/l) occurred in one female patient at month 2. With the exception of corticotherapy (prednisone 10 mg/day), all medications were discontinued (nonathymulin, piroxicam 30 mg/day, aspirin 3 g/day). Bone marrow examination showed the presence of numerous megakaryocytes. Spontaneously, the platelet count rose to $75 \times 10^9/l$ two weeks later and $200 \times 10^9/l$ six weeks later. Six months after nonathymulin withdrawal severe thrombocytopenia recurred with ecchymosis and haemorrhages prompting us to increase the corticosteroid dosage to 1 mg prednisone/kg/day. Another patient experienced paraesthesiae of the legs at month 5 without any other neuromuscular disturbance or dermatological lesions. Neuromuscular biopsy showed the presence of vasculitis. Nonathymulin treatment was discontinued; pulse corticosteroid and immunosuppressive therapy (chlorambucil) dramatically improved the clinical condition.

In the second trial two out of the 15 patients

Table 3 Changes in clinical variables between entry and conclusion of the trials, by treatment group

Variable	First trial				Second trial			
	Thy 1 mg (n=15)	p Value*	Placebo (n=15)	p Value*	Thy 5 mg (n=14)	Placebo (n=12)	p Value*	Thy 10 mg (n=12)
Morning stiffness (min)	-46 (143)†	NS	+1.0 (141)	NS	-38 (67)	-38 (133)	NS	-71 (124)
Grip strength (mmHg)	-9 (174)	NS	-39 (163)	<0.03	+75 (138)	-111 (275)	NS	-89 (272)
PIP joint circumference (mm)	0 (11)	NS	-1 (19)	NS	-7 (14)	-7 (16)	NS	-5 (13)
Lee index	0 (5)	NS	0.5 (5)	<0.05	-6 (7)	-2 (5)	NS	-3 (4)
Ritchie index	-5 (5)	NS	-4 (7)	<0.05	-6 (7)	-4 (6)	NS	-7 (7)
Pain (on 100 mm visual analogue scale)	-9 (34)	NS	-6 (35)	NS	-20 (12)	-6 (27)	NS	-18 (20)
Swollen joints (number)	-3 (5)	NS	-1 (6)	NS	-5 (6)	0 (4)	NS	-4 (4)
Prednisone consumption (mg/day)	0 (3)	NS	+1 (0)	<0.05	-2 (4)	+2 (3)	NS	0 (2)
Patient self assessment	-2.2 (2)	<0.05	-1.3 (3)	<0.02	+1.2 (2)	-0.3 (3)	NS	+1.4 (2)

*Statistical significance of the changes in the variables between placebo and treated group was determined by the Mann-Whitney U test. (In the first trial the Kruskal-Wallis test did not demonstrate any significant difference except for the patient self assessment.)

†Values are mean (SD).

Table 4 Immunological status of patients with RA at the start of the trial/subsequent changes during the trial

Variables*	Treatment group		
	Placebo	Thy 1 mg	Thy 5 mg
T3 subsets (69.5 (11.5))	54 (12)/-7 (21)†	50 (11)/-2 (12)	53 (11)/-1 (15)
T4 subsets (47 (9.9))	41 (9)/-4 (11)	36 (12)/1 (9)	37 (10)/-4 (13)
T8 subsets (30 (8.25)) H3H31	14 (5)/-0.2 (4)	13 (7)/0.3 (5)	16 (6)/-0.1 (8)
T4/T8 ratio (1.7 (0.5))	3.3 (1.3)/-0.1 (1.5)	3.3 (2.3)/-0.5 (1.4)	3.0 (2.3)/-0.4 (2.1)
Suppressive T cell function§			
Normal	4/4 ‡	3/3 ‡	10/9 ‡
Defective	11/11	13/13	6/7

*Value in parentheses in this column are those for control subjects.

†Values are mean (SD).

‡p<0.025.

§Numbers at the start and the end of the trial.

receiving nonathymulin were withdrawn from the study because of side effects. A few minutes after the first injection one patient experienced a 'malaise' with low blood pressure, and laryngeal oedema, which resolved within 30 minutes after an intravenous corticosteroid injection. The second patient was withdrawn from the study at month 1 because of painful injections.

It is worth noting that local painful injection occurred in nine of the patients in the first trial, resulting in withdrawal in one case, and in all the patients in the second trial, resulting in withdrawal in three. These painful injections were not only more frequent but also more severe in the second trial than in the first.

IMMUNOLOGICAL DATA (FIRST TRIAL)

At the start of the trial T cell subsets were the same in the three groups, showing a clear cut increase in the OKT4+/T8+ ratio (>2.5) in 30-40% of patients (see Table 4). At variance, as stated above, the

three groups differed with regard to the suppressor T cell function since 10 out of 16 patients in the nonathymulin 5 mg group were considered to have normal suppressor cell function compared with only three in the nonathymulin 1 mg group, and four in the placebo group (p<0.025).

Only minor changes in the remaining immunological parameters were observed during the trial in all patient groups, without a definite trend. An interesting correlation was noted, however, between the immunological status of patients and their individual response to treatment. Whereas the OKT4+/T8+ ratio at the start of the trial was not a predictive criterion for the clinical response to nonathymulin treatment, the average of the four determinations made during the trial was higher in the patients showing clear clinical response (i.e., good or very good results) to nonathymulin (see Table 5).

Moreover, seven of the eight patients showing clear clinical response had normal suppressor T cell function at entry, whereas this was the case in only six out of the 24 non- or poorly responsive patients (see Table 5), suggesting that a normal suppressive T cell activity in these experimental conditions might be a predictive criterion for the clinical response to nonathymulin treatment.

Discussion

These results suggest that nonathymulin is of benefit to patients suffering from well established rheumatoid arthritis (mean duration of the disease 13 years). The proportion of patients achieving moderate or very good overall improvement is higher in patients receiving nonathymulin than in patients receiving placebo. The difference reaches significance in the first trial (p<0.02). Statistically significant differences are also noted for several important

Table 5 Dependence of the clinical response to nonathymulin on the T4+/T8+ ratio and the suppressive T cell function in Thy 1 and Thy 5 groups

Variable	No clinical improvement†	Clinical improvement†
T4/T8		
<2.5	11	1
>2.5	11	7
ND	2	0
T cell suppressive function		
Normal	6 *	7
Defective	18	1

*=Fisher's exact test, p=0.0032.

†No clinical improvement = nil or moderate results, clinical improvement = good or very good result.

ND=not determined.

individual parameters (grip strength, Lee index). It is important to stress the significant though modest effect on steroid consumption since one may assume that the other effects of nonathymulin have been partly blurred by the decrease of steroid dosage in patients showing clinical improvement. The analysis of the second trial is complicated by the difference in daily corticosteroid consumption noted between the two groups at the start of the trial and by the small number of patients included in the study. In the two trials the approximate 90% confidence interval for the difference in true response probabilities favours nonathymulin. The clinical improvement was more clear cut when using nonathymulin 5 mg rather than nonathymulin 1 mg three times a week. At variance, the rate of improvement was not further increased by using nonathymulin at 10 mg a day, suggesting that the dosage of 5 mg three times a week is sufficient for optimal effect. One cannot exclude the possibility that giving the compound more frequently would not be more efficient. This hypothesis would be in keeping with the relatively short half life of nonathymulin (30–60 min), even if the duration of the drug effect on T lymphocytes is much longer (24–48 h³).

Minor side effects were noted. Local pain was common at 10 mg and was probably due to the zinc salts since it was also observed with the placebo preparation containing zinc. It was rare in the other groups. Thrombocytopenia and vasculitis were observed in two cases of the 5 mg group. They probably represented complications of the disease rather than an adverse drug reaction since they recurred long after treatment cessation. The malaise noted in one case (10 mg/day) after the first injection is more difficult to interpret. An allergic reaction is unlikely because of the small molecular weight of the peptide. It should be noted that such a reaction has never been observed in more than 150 other patients treated with nonathymulin (unpublished data).

The potential clinical benefit of nonathymulin in RA is obviously linked to its low toxicity compared with that of other drugs that often appear more efficient than the peptide but are also more toxic (e.g., D-penicillamine,¹⁴ tripronin,¹⁵ gold salts). Although it is impossible to make a direct comparison, results presented here indicate that nonathymulin could be at least as efficient as other immunomodulators also used in RA (e.g., thymopentin,² levamisole¹). More data are needed to confirm its clinical efficacy, which might be improved by the use of other administration schedules, notably daily doses. In this regard the search for other routes of administration (perlingual, percutaneous) should be encouraged.

The mode of action of nonathymulin in RA is open to speculation. The most likely interpretation is a stimulation of suppressor T cell function as observed in several experimental models³ and in murine lupus.¹⁶ The fact that clinical improvement was more often noted in patients with a high T4+/T8+ ratio fits with this hypothesis, but the correlation of normal suppressor cell function with nonathymulin responsiveness apparently contradicts this last statement. In any case the interest of the correlation between clinical response to an immunomodulation and immunological status, noted in this trial, should be emphasised and prompt further immunological studies.

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