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Confirmative Study of the Effectiveness of Thymopentin in Active Rheumatoid Arthritis

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Introduction

The biologic effects of thymopentin have recently been reviewed in a summary paper [1]. The effect of thymopentin on T lymphocytes has been one of the reasons for investigation into the influence of thymopentin on rheumatoid arthritis (RA), as disturbances in cellular immunity have been identified in this disease. Indeed, an unbalanced ratio between helper cells and suppressor-cytotoxic cells has been evidenced, with an absolute or relative excess of helper T cells and a decrease in suppressor and cytotoxic cells [2]. The thymopentin molecule has a plasma half-life of 30 s [3] and is broken down to natural amino acids by peptidases which are abundant in human plasma. Despite its brief half-life, a single intravenous dose has been reported to effect cellular processes in T lymphocytes, lasting more than 5 days [4].

In several former studies it has been attempted to find the optimum dose level and the appropriate route of administration. In this connection, the following regimens were tested: subcutaneous injection of 1, 10, and 50 mg three times a week [5]; intramuscular injection of 1 mg/week [5, 6]; intravenous injection of 10 mg three times a week [7]; 50 mg/week [5, 6, 8], and 100 mg/day (10 × 10 mg) for 3 consecutive weeks [9]. As it turned out, none of these regimens was optimal.

On the other hand, a recently conducted pilot study using 50 mg i.v. as prolonged injection (10 min) three times weekly reported very encouraging results [10]. We, therefore, decided to treat our patients according to a similar protocol.

As for other biologically active small peptides (such as the gonadotropin-releasing

hormone or the thyrotropin-releasing hormone) [11], the duration of the injection should be long enough to reach the respective receptors, but the stimulation should not be too prolonged and/or too intense to avoid desensitization (downregulation phenomenon). As in the cited open study [10], a prolonged intravenous injection of thymopentin was, therefore, chosen. Since one of the major complaints of patients presenting with RA is chronic pain (a subjective parameter), and since repeat intravenous injections per se can have a powerful placebo effect, a controlled double-blind randomized study was undertaken.

Table I. Characteristics of patients

Parameter	Thymopentin	Placebo
Number	21	20
Age, years (mean)	56.1	52.7
Sex	19 F/2 M	18 F/2 M
Weight, kg (mean)	69	59.1
ARA functional class		
I (complete)	2	0
II (adequate)	8	8
III (limited)	11	11
IV (incapacitated)	0	1
Disease duration, years (mean)	9.75	10.6
Nonsteroidal anti-inflammatory drugs	21	20
Steroids	8	10

Patients and Methods

Patients

Forty-one patients suffering from classical or definite chronic RA [12] entered the study: 21 patients received thymopentin and 20 placebo. The initial characteristics of the 41 patients, i.e., age, sex, disease duration, functional classification of *Steinbrocker* et al. [13], and concomitant treatment, are illustrated in table I.

Criteria for admission were: evidence of active disease defined as showing six or more swollen joints and two of the following criteria: (1) morning stiffness for 45 min or longer; (2) presence of nine or more joints tender on pressure or painful on motion, and (3) sedimentation rate of 20 mm or more at the 1st h.

For patients already on medication a washout period of 3 months was required for the following drugs: gold, cytotoxic drugs, hydroxychloroquine, *d*-penicillamine, levamisole, and all other slow-acting drugs; a washout period of 1 month was required for phenylbutazone. Background therapy with nonsteroidal antiinflammatory drugs or aspirin and corticosteroids (less than 12 mg of prednisolone per day) was not desirable, but accepted if necessary.

Drug Supply and Medication

Thymopentin and placebo (physiological saline solution) were provided in coded, unidentifiable 5-ml multidose vials (thymopentin 100 mg/ml or placebo). 0.5 ml of test drug was diluted with saline to 10 ml, and the dilution was injected intravenously over 10 min. The 1st, ml was given by intravenous push and the remaining 9 ml in the following 10 min (i.e., 1 ml as push/min). The dosing was repeated three times per week for 3 consecutive weeks.

Clinical Assessment

The clinical assessment included complete joint evaluation: (1) number of joints with pain at rest; (2) number of joints with pain on motion; (3) scores for tenderness on pressure – index of *Ritchie* et al. [14]: 0 = none, 1 = mild (positive response on questioning), 2 = moderate (spontaneous response), 3 = severe (patient withdraws on examination); (4) scores for swollen joints: 0 = none, 1 = mild (detectable synovial thickening without loss of bone contours), 2 = moderate (loss of distinctness of bone contours), 3 = severe (bulging synovial proliferation with cystic character); (5) assessment of pain and severity of pain on awakening, measured by a visual analogue scale; (6) morning stiffness; (7) grip strength (left and right hand); (8) scoring of the disease activity (5 grades) assessed by both the investigator and the patient, and (9) assessment of the therapeutic effect. Evaluations were realized at start and after 3 weeks of therapy.

Table II. Global clinical assessment of thymopentin and placebo efficacy, respectively (investigator's judgment)

Treatment	Worse	Unchanged	Improved			Mann-Whitney test
			minimal	moderate	marked	
Thymopentin	1	3	3	9	5	
Placebo	4	7	3	5	1	$p = 0.0083$

Safety Laboratory Assessments

Hematological investigations and clinical chemistry were performed at the start and 3 and 7 weeks later in all cases.

Statistical Methods

The mean values for all of the above-mentioned clinical assessments were calculated at the beginning and at the end of the 3-week treatment. The intragroup changes in the values observed between start and end of the therapy were statistically analyzed by Wilcoxon matched-pair tests. For statistical analysis of the differences between the two treatment groups the Mann-Whitney test was used.

Results

In table I the main characteristics of both populations studied are compiled. Prior to treatment, both groups were comparable with regard to all listed parameters ($p > 0.10$), except for weight ($p = 0.013$) where higher values were found in the thymopentin group. In addition, both groups were comparable with regard to all clinical parameters assessed ($p > 0.10$), except the Ritchie index which was higher in the placebo group ($p = 0.049$) than in the group assigned to thymopentin treatment.

The clinical examination performed after 3 weeks of thymopentin treatment revealed statistically significant improvement in the following parameters: (1) number of joints painful at rest ($p < 0.01$); (2) number of joints painful on motion ($p < 0.05$); (3) scores for tenderness on pressure (Ritchie index; $p < 0.001$); (4) scores for swollen joints ($p < 0.01$); (5) assessment of pain ($p < 0.01$); (6) assessment of severity of pain on awakening ($p < 0.001$); (7) grip strength, right hand ($p < 0.05$), and (8) morning stiffness ($p < 0.05$). On the contrary, no improvement was noted in the placebo-treated group, except for morning stiffness ($p < 0.05$).

An intergroup comparison (thymopentin versus placebo) showed statistically significant differences – favoring thymopentin treatment – in the following parameters: (1) scores for tenderness on pressure (Ritchie index; $p < 0.05$, one-tailed test); (2) scores for swollen joints ($p < 0.05$); (3) grip strength, right hand ($p < 0.05$, one-tailed test); (4) assessment of pain ($p < 0.01$); (5) assessment of severity of pain on awakening ($p < 0.05$), and (6) improvement in disease activity judged by investigator ($p < 0.01$) and by patients ($p < 0.001$).

The overall assessment of therapeutic effect is illustrated in table II. Changes in the mean values of laboratory parameters – if present at all – remained within the normal range, and detailed analysis of the values revealed no differences between the thymo-

Table III. Compilation of side effects

Side effect	n
Thymopentin	
Menstrual flow stronger than usual	1
Itching at the site of injection and on the upper arm (during the whole study)	1
Hypersomnia	4
One single occasion	2
During the 1st week	1
During the 2nd week	1
One single occurrence of nausea and vomiting; dysesthesia during the 1st and the 2nd week	1
Placebo	
Asthenia during the whole study	1
Transpiration and dyspnea during the injection throughout the study	1

pentin and the placebo group. Side effects reported during the 3-week study are listed in table III. In 7 cases of the thymopentin group and in 2 cases of the placebo group minor side effects were registered; no patient had to be dropped on that account.

Discussion

Compared with placebo, statistically significant improvement was observed with thymopentin in active RA in most of the tested clinical parameters after 3 weeks of therapy. The present double-blind study thus confirms the results observed in a previously conducted open study in RA patients using the same treatment regimen [10].

The rapid onset of clinical improvement is in contrast to the classical disease-modifying antirheumatic drugs whose beneficial clinical effect only appears with a delay of about 3 months.

Thymopentin possibly represents a new approach to the therapy of RA. Although the mechanism of action is still unknown, the molecule possibly acts through its immunomodulatory properties elicited by stimulation of suppressor mechanisms. We believe that the route of administration and the dose regimen are crucial for the bioavailability of the drug in order to reach appropriate target cells. As the molecule has a half-life of only 30 s in human serum, the prolonged intravenous injection (over 10 min) of 50 mg of thymopentin three times a week might facilitate the drug's ability to reach the receptors at the cellular level and thus induce its biological effects. This hypothesis finds some support in the present randomized double-blind study, and may very well be the reason why previous studies [5–9] found none or – at best – suboptimal response. Additionally, in one particular study [9], the phenomenon of 'downregulation' [11] might have played a negative role as well.

No serious adverse effects were observed. Most of the reported unexpected drug experiences were probably nonspecific in nature and should in no way limit the use of thymopentin as an alternative treatment of active RA. (Only hypersomnia may be a specific feature of thymopentin; this remains a possibility due to the drug's known effect on neuromuscular transmission.)

The excellent safety profile of thymopentin has also been reported by other authors [5–8]. Absence of serious side effects and rapid onset of clinical improvement – in contrast to the classical disease-modifying antirheumatic drugs – speak in favor of thymopentin in the treatment of active RA.

Summary

Forty-one patients with active rheumatoid arthritis entered a controlled double-blind randomized study. Of these patients, 21 received prolonged intravenous injections (10 min) of thymopentin 50 mg three times a week for 3 consecutive weeks, whereas 20 received placebo. Both groups were comparable with regard to clinical parameters. No immunological tests were performed. Analysis of the results after 3 weeks showed that the improvement in the thymopentin group was statistically significant ($p < 0.05$ or $p < 0.01$) for all clinical parameters, except for the left-hand grip strength. On the other hand, no significant improvement was observed for any parameter, except morning stiffness, in the patients on placebo. The intergroup comparison showed statistically significant differences, favoring thymopentin over placebo treatment, in the Ritchie index, the scores of swollen joints, the assessment of severity of pain, and the scores for changes in the activity of the disease. The present placebo-controlled double blind study thus confirms the positive results generated in a similar open study, i.e., the beneficial therapeutic effect of prolonged intravenous injections of thymopentin in patients with severe rheumatoid arthritis. The drug appears to be safe at the dose regimen used.

Résumé

Quarante et un patients atteints de polyarthrite rhumatoïde en activité ont participé à une étude contrôlée randomisée, à double insu; 21 d'entre eux ont reçu 3 fois par semaine et pendant 3 semaines consécutives une injection intraveineuse lente (10 min) de 50 mg de thymopentine, les 20 autres recevant un placebo. Les deux groupes étaient comparables quant aux paramètres cliniques. On n'a pas effectué de tests immunologiques.

L'analyse des résultats obtenus en 3 semaines a montré que l'amélioration dans le groupe «thymopentine» était statistiquement significative ($p < 0,05$ ou $p \leq 0,01$) pour tous les paramètres cliniques, à l'exception de la force de serrage de la main gauche. Dans le groupe placebo d'autre part, on n'a observé aucune amélioration significative, à l'exception de la raideur matinale. La comparaison inter-groupes a révélé en faveur de la thymopentine des différences statistiquement significatives en ce qui concerne l'indice de Ritchie, l'enflure articulaire, l'intensité de la douleur et les scores de modification de l'activité de la maladie.

La présente étude à double insu contre placebo confirme donc les résultats positifs obtenus au cours d'une étude ouverte similaire, c'est-à-dire l'effet thérapeutique bienfaisant d'injections intraveineuses lentes de thymopentine à des patients atteints de polyarthrite rhumatoïde grave. Le médicament paraît sûr avec le régime posologique utilisé.

Zusammenfassung

Einundvierzig Patienten mit chronisch progredienter Polyarthritis wurden in eine kontrollierte, randomisierte Doppelblindstudie aufgenommen; 21 Probanden erhielten verlängerte (10 min) intravenöse Injektionen von 50 mg Thymopentin 3mal wöchentlich während 3 aufeinanderfolgender Wochen; 20 Patienten erhielten Plazebo. Die beiden Gruppen waren im Hinblick auf die klinischen Parameter vergleichbar. Immunologische Tests wurden nicht durchgeführt. Die Analyse der Ergebnisse nach 3 Wochen zeigte, dass die Besserung in der mit Thymopentin behandelten Gruppe statistisch signifikant war ($p < 0,05$ oder $p < 0,01$); dies bezog sich auf alle klinischen Parameter ausser auf die Griffkraft der linken Hand. Bei den mit Plazebo behandelten Patienten trat bei keinem der untersuchten Parameter eine signifikante Besserung ein, ausser bei der Morgensteifigkeit. Der Vergleich zwischen den beiden Gruppen ergab statistisch signifikante Unterschiede zugunsten von Thymopentin gegenüber Plazebo im Ritchie-Index, in den Scores für geschwollene Gelenke, in der Einschätzung und Intensität des Schmerzes sowie in den Scores für Änderungen in der Aktivität der Krankheit. Die vorliegende plazebokontrollierte Doppelblindstudie bestätigt somit die positiven Ergebnisse einer ähnlichen offenen Studie, d.h. den vorteilhaften therapeutischen Effekt von verlängerten intravenösen Injektionen von Thymopentin bei Patienten mit schwerer progredienter Polyarthritis. Bei Einhaltung des empfohlenen Regimes erscheint das Medikament als unbedenklich.

Riassunto

Quarantuno pazienti affetti da poliartrite reumatoide hanno partecipato ad uno studio in parallelo sotto controllo; 21 di questi sono stati trattati tre volte

alla settimana, durante 3 settimane di seguito, un'iniezione i.v. lenta (10 min) di 50 mg di thymopentine; gli altri 20 sono stati trattati con un placebo. I due gruppi erano paragonabili per ciò che concerne i loro parametri clinici. Non vennero effettuati dei testi immunologici. L'analisi dei resultati ottenuti durante tre settimane ha mostrato che il miglioramento nel gruppo trattato con la thymopentine era statisticamente significativo ($p < 0,05$ o $p < 0,01$) per tutti i parametri clinici ad eccezione di quello basato sulla forza della «stretta di mano» della mano sinistra. Nel gruppo dei pazienti trattati con placebo non si potè costatare alcun miglioramento significativo all'eccezione della rigidità mattinale. Il confronto fra i due gruppi ha messo in evidenza in favore della thymopentine delle differenze statisticamente significative per ciò che concerne l'indice di Ritchie, il gonfiore articolare, l'intensità del dolore e i tassi di modificazione dell'evoluzione della malattia. Questo studio comparativo in parallelo tra pazienti trattati con il farmaco ed altri unicamente con placebo conferma dunque i risultati positivi ottenuti nel corso d'uno studio aperto simile, vale a dire l'effetto terapeutico benefico ottenuto iniettando i.v. lentamente la thymopentine a pazienti affetti da poliartrite reumatoide grave. Il medicamento sembra dare tutte le assicurazioni allorchè viene somministrato secondo la posologia indicata.

Resumen

Cuarenta y un pacientes afectos de artritis reumatoide activa ingresaron en un estudio randomizado, controlado y doble ciego; 21 recibieron una inyección i.v. prolongada (10 min) de timopentina 50 mg, 3 veces semanales durante 3 semanas consecutivas, mientras que 20 recibieron placebo. Los dos grupos fueron comparables por lo que se refiere a los parámetros clínicos. No se efectuó ningún ensayo inmunológico. El análisis de los resultados al cabo de 3 semanas mostró que la mejoría fue estadísticamente significativa en el grupo de timopentina ($p < 0,05$ o $p < 0.01$) en todos los parámetros clínicos, con excepción de la fuerza de prensión de la mano izquierda. Por otra parte, en los pacientes con placebo no se observó ninguna mejoría significativa en ningún parámetro con excepción de la rigidez matinal. La comparación entre los grupos mostró diferencias estadísticamente significativas a favor de la timopentina respecto del tratamiento con placebo, en el índice de Ritchie, las puntuaciones de las articulaciónes inflamadas, la evaluación y la gravedad del dolor, así como en las puntuaciones para los cambios en la actividad de la enfermedad. Así, este estudio doble ciego con placebo como control confirma los resultados positivos obtenidos en un estudio abierto análogo, a saber, el efecto terapéutico benéfico de las inyecciones i.v. prolongadas de timopentina en pacientes afectos de artritis reumatoide grave. El fármaco es inocuo a la dosis administrada.

References

1 Goldstein, G.; Audhya, T.K.: Thymopoietin to thymopentin: experimental studies. Surv. immunol. Res. *4:* suppl. 1, pp. 1–10 (1985).

2 Veys, E.M.; Hermans, P.; Schindler, J.; Kung, P.C.; Goldstein, G.; Symoens, J.; Van Wauwe, J.: Evaluation of T cell subsets with monoclonal antibodies in patients with rheumatoid arthritis. J. Rheumatol. *9:* 25–29 (1982).

3 Tischio, J.P.; Patrick, J.R.; Weintraub, H.S.; Chasin, M.; Goldstein, G.: Short in vitro half-life of thymopoietin$_{32-36}$ pentapeptide in human plasma. Int. J. Peptide Protein Res. *14:* 479–484 (1979).

4 Di Perri, T.; Laghi-Pasini, F.; Auteri, A.: Immunokinetics of a single dose of thymopoietin pentapeptide. J. Immunopharmacol. *2:* 567–572 (1980).

5 Veys, E.M; Huskisson, E.C.; Rosenthal, M.; Vischer, T.L.; Mielants, H.; Thrower, P.A.; Scott, J.; Ott, H.; Scheijgrond, H.; Symoens, J.: Clinical response to therapy with thymopentin (TP-5) in rheumatoid arthritis. Ann. rheum. Dis. *41:* 441–443 (1982).

6 Rosenthal, M.; Huskisson, E.C.; Veys, E.; Vischer, T.L.: Thymopoietin bei der Behandlung der chronischen Polyarthritis. Verh. dt. Ges. Rheumatol. *7:* 400–403 (1981).

7 Horwitz, D.A.; Glynn, M.J.; Barada, F.A.; Andrews, B.S.; O'Brien, W.; Kay, H.D.; Schindler, J.; Goldstein, G.: Effects of thymopoietin$_{32-36}$ (TP-5) in rheumatoid arthritis: a preliminary report; in Krakauer, Cathcart, Immunoregulation and autoimmunity; 13th ed., pp. 231–240 (Elsevier, Amsterdam 1980).

8 Thrower, P.A.; Doyle, D.V.; Scott, J.; Huskisson, E.C.: Thymopoietin in rheumatoid arthritis. Rheumatol. Rehabil. *21:* 72–77 (1982).

9 Veys, E.M.; Mielants, H.: Thymopoietin pentapeptide (TP-5) in the treatment of rheumatoid arthritis (Abstract). Fourth Eular Workshop on Rheumatology Research. Clin. Rheumatol. *3:* 110 (1984).
10 Franchimont, P.; Hauwaert, C.; Bolla, K.: Thymopentin in active rheumatoid arthritis. An open monitored study in 16 patients. Surv. immunol. Res. *4:* suppl. 1, pp. 81–86 (1985).
11 Sharpe, R.M.: HCG-induced decrease in availability of rat testis receptors. Nature, Lond. *264:* 644–646 (1976).
12 Bunim, J.J.: Revision of diagnostic criteria in rheumatoid arthritis. Bull. rheum. Dis. *9:* 175–176 (1958).
13 Steinbrocker, O.; Traeger, Ch.: Battermann, R.C.: Therapeutic criteria in rheumatoid arthritis. J. Am. med. Ass. *140:* 659–663 (1949).
14 Ritchie, D.M.; Boyle, J.A.; McInnes, J.M.; Jasani, M.K.; Dalakos, I.G.; Griveson, P.; Buchanan, W.: Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. Q. Jl Med. *37:* 393–406 (1968).

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