Treatment of Cutaneous T-Cell Lymphomas with TP-5*

Evaluation of the Clinical Effect in 8 Patients

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* Dedicated to Prof. H. Kresbach, Graz, in honour of his 60th birthday.

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Eight patients with cutaneous T-cell lymphomas (6 patients with mycosis fungoides, 1 patient with Sézary's syndrome, 1 patient with low-grade malignant lymphoma, unclassified) were treated with TP-5, a synthetic pentapeptide having the same biologic activity as the thymic hormone thymopoietin. TP-5 was administered three times weekly at a dosage of 50 mg subcutaneously in 6 patients, 50 mg intravenously in 1 patient, and 100 mg subcutaneously in 1 patient. Clinical evaluation at the end of the trial disclosed improvement in 4 patients (2 patients with mycosis fungoides, 1 patient with Sézary's syndrome, 1 patient with low-grade malignant lymphoma, unclassified), deterioration in 3 patients with mycosis fungoides and no change in 1 patient with mycosis fungoides. As TP-5 evidently exerts some effect on cutaneous T-cell lymphomas, further investigations of its therapeutic potential in this group of diseases seem worthwhile.

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TP-5, a synthetic pentapeptide corresponding to the amino acid residues 32–36 of the thymic hormone thymopoietin, displays the biologic activity of the whole molecule in a number of assays (1, 2). In laboratory experiments thymopoietin has been shown to promote selectively the differentiation of T-cells while inhibiting B-cells (3), and to influence granulocyte differentiation (4). Furthermore, TP-5 induces suppressor cell function in mice with autoimmune disease (5), and appears to regulate the immune answer by balancing the responsiveness (6). Therapeutic application of TP-5 in humans suffering from diseases characterized by deviations of the immune system yielded favorable effects in a number of cases (7, 8, 9, 10, 11).

We report here on the clinical results of a therapeutic trial with TP-5 in 8 patients suffering from cutaneous T-cell lymphoma. The outcome of the study was inconsistent, as 4 patients improved, 3 patients grew worse, and 1 patient's status was not altered. Yet the results indicate that cutaneous T-cell lymphomas may be influenced in some way by TP-5, thus rendering further investigations promising.

PATIENTS AND TREATMENT

Eight patients (6 males, 2 females) with cutaneous T-cell lymphoma (initial plaque stage of mycosis fungoides in 3 patients, plaque stage of mycosis fungoides in 3 patients, Sézary's syndrome in 1 patient, low-grade malignant lymphoma, unclassified, in 1 patient) lacking manifest lymph node and/or systemic involvement were treated with TP-5 after written informed consent had been obtained. TP-5 was applied three times a week on alternate days (usually on Monday, Wednesday, Friday) at a dose of 50 mg subcutaneously in 6 patients, 50 mg intravenously in 1 patient, and 100 mg subcutaneously in 1 patient. The duration of the trial, having been planned to be 6 weeks, was extended in 4 patients with favourable results after the initial course. At about weekly intervals the therapeutic effect was assessed by estimating the week-to-week change in the patient's disease status

Table I. *Clinical data on 8 patients with cutaneous T-cell lymphoma treated with TP-5*
PUVA = photochemotherapy (8-Methoxypsoralen+UVA); GCS = glucocorticosteroids

Case no.	Sex	Age (years)	Diagnosis	Duration of disease (years)	Specific therapy prior to TP-5	Topical GCS during trial with TP-5
1	Female	60	Initial plaque-stage mycosis fungoides	3	PUVA Topical GCS	No
2	Male	68	Initial plaque-stage mycosis fungoides	5	None	No
3	Male	71	Initial plaque–stage mycosis fungoides	1	Topical GCS	Yes
4	Male	42	Plaque-stage mycosis fungoides	10	Unspecified ointments	No
5	Male	48	Plaque-stage mycosis fungoides	8	Topical GCS	No
6	Male	56	Plaque-stage mycosis fungoides	10	Topical GCS	Yes
7	Male	74	Sézary's syndrome	3	Chlorambucil 4 mg, Methylprednisolone 40 mg, gradually tapered	Yes
8	Female	53	Low-grade malignant T-cell lymphoma, unclassified	5	Topical GCS; Chlorambucil 4 mg, Methylprednisolone 40 mg, gradually tapered	Yes

and by evaluating the percentage and morphologic presentation of the involved skin. If needed, emollients were used for additional skin treatment; in 4 patients topical glucocorticosteroids had to be applied, at least temporarily.

For safety reasons, routine laboratory tests (hematologic tests, clinical chemistry, urine analysis), and serological test (immunoglobulins, complement factors, C3-proactivator, C-reactive proteins, a_1-antitrypsin, antinuclear antibodies, immune complexes) were performed. The delayed type skin hypersensitivity to recall antigens (tetanus, diphtheria, streptococcus, tuberculine, candida, trichophyton, proteus) was assessed before and during the trial in 6 patients using the Multitest® method (Mérieux).

Detailed clinical data of the patients treated are presented in Table I. After the withdrawal of TP-5, conventional therapy according to the disease state was reinstalled.

RESULTS

In 4 patients with favorable responsiveness initially the trial was extended up to 8, 10, 12 and 13 weeks, respectively. The final results were a moderate to good effect in 1 patient with plaque stage mycosis fungoides, a moderate improvement in 1 patient with plaque-stage mycosis fungoides and 1 patient with low-grade malignant T-cell lymphoma, unclassified, and no change in 1 patient with initial plaque-stage mycosis fungoides. 2 patients (1 with initial plaque-stage mycosis fungoides, 1 with plaque-stage mycosis fungoides) had grown worse at the end of the 6 weeks' course, and the drug was withdrawn as planned. In 1 patient with initial plaque-stage mycosis fungoides, TP-5 had to be abandoned after 5 weeks because of continuous deterioration of the condition. Specific involvement of lymph nodes became apparent in the patient with Sézary's syndrome after 2 weeks, and the treatment was discontinued. At this time the skin lesions had improved slightly. Details of the 8 patients' disease course during the trial with TP-5 are shown in Table II.

Table II. *Clinical effect of treatment with TP-5 in 8 patients with cutaneous T-cell lymphoma*

CH = clincal evaluation of week-to-week change: 0 = no change; b = improved; (b) = minimally improved; w = worse; – = not done; E = erythema (% involvement of body surface); P = plaque (% involvement of body surface); T = tumour (number)

Case no.	Dosage of TP-5, 3 times weekly/ Mode of application/ Duration of therapy		At start	Assessment of skin involvement after week I	II	III	IV	V	VI	Further weeks		General outcome	Side effects[a]
1	100 mg	CH:		0	w	–	w	–	w			Deterio-	Flare-up reaction
	Subcutaneous	E:	2	2	2.5	–	3	–	3			ration	Pruritus
	6 weeks	P:	0	0	0	–	0	–	0				Sensation of heat
										VII	VIII		
2	50 mg	CH:		w	(b)	–	0	0	(b)	0	w	No change	Vasovagal reac-
	Intravenous	E:	12	12	10	–	10	10	10	10	10		tion during
	8 weeks	P:	0	0	0	–	0	0	0	0	0		injection
3	50 mg	CH:		b	(b)	(b)	w	w				Deterio-	Dizziness
	Subcutaneous	E:	25	25	25	25	18	15				ration	Restlessness
	5 weeks	P:	0	0	1?	1?	7	10					Pressure in
		T:	0	1?	1?	1?	1?	1	(2?)	XII			the head
4	50 mg	CH:		(b)	(b)	(b)	w	(b)	(b)	(b)		Moderate	Tiredness
	Subcutaneous	E:	12	16	16	14	14	14	14	14		to good	Headaches
	12 weeks	P:	4	0	0	0	0	0	0	0		improve-	
												ment	
5	50 mg	CH:		0	(b)	(b)	w	w	w			Deterio-	None
	Subcutaneous	E:	4	4	6	7	9	3	3			ration	
	6 weeks	P:	6	6	4	3	3	9	10	IX	XII		
6	50 mg	CH:		0	b	b	0	(b)	(b)	(b)	w	Moderate	None
	Subcutaneous	E:	1	1	5	5	5	7	5	5	5	improve-	
	13 weeks	P:	9	9	5	5	5	3	2	2	2	ment	
7	50 mg	CH:		(b)	(b)							Slight	None
	Subcutaneous	E:	100	100	100							improve-	
	2 weeks	P:	0	0	0							ment	
										IX	XII		
8	50 mg	CH:		0	b	w	–	b	(b)	b	(b)	Moderate	None
	Subcutaneous	E:	92	92	96	94	–	94	94	64	20	improve-	
	10 weeks P, papules:		8	8	4	6	–	6	6	5	15	ment	
											1 tumour		

[a] With exception of the flare-up reaction in patient 1 the side effects were not attributable to the treatment with certainty.

The only side effect attributable with some certainty to the drug was a temporary flare-up reaction of the skin lesions in the patient treated with the 100 mg dose of TP-5. For other complaints during the trial, see Table II. The monitoring of laboratory data did not disclose any consistent change in values during therapy.

Delayed-type skin hypersensitivity to recall antigens could be followed in 6 patients. Reactivity, measured as summed diameters of the infiltrations present at the 48-hour evaluation, was found to be enhanced in 5 patients under TP-5, with a decline in 2 patients after further treatment. In 1 patient a slight reduction in skin reactivity occurred during the trial. Data concerning delayed-type skin hypersensitivity to recall antigens are presented in Fig. 1.

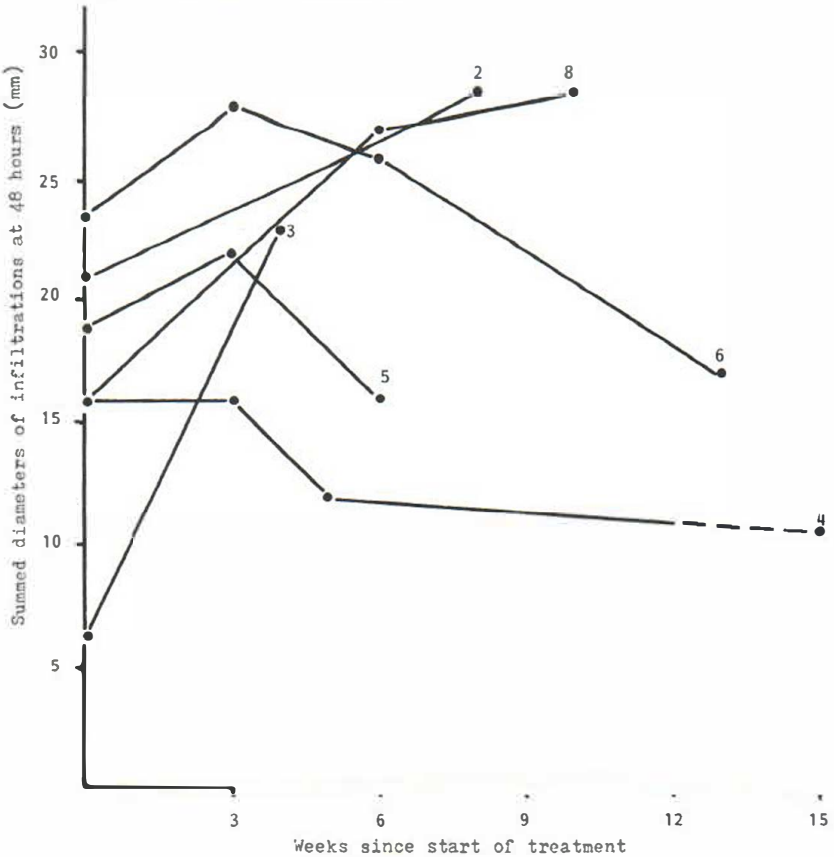

Fig. 1. Development of delayed type skin hypersensitivity to 7 recall antigens (tetanus, diphtheria, streptococcus, tuberculine, candida, trichophyton, proteus) applied with the Multitest® method (Merieux) in 6 patients treated with TP-5. —— = treatment; --- = off treatment; 2, 3, 4, 5, 6, 8 = case-no. (for identification see Table I).

DISCUSSION

Inconsistent clinical results were obtained when 8 patients suffering from cutaneous T-cell lymphoma (6 patients with plaque-stage mycosis fungoides, 1 patient with Sézary's syndrome, 1 patient with low-grade malignant T-cell lymphoma, unclassified) were treated with TP-5. A good to moderate effect was evident in 1 patient, moderate improvement occurred in 3 patients, no change could be seen in 1 patient, and the disease status of 3 patients was found to have grown worse. Nevertheless, 7 out of 8 patients experienced at least some improvement in the beginning, which was followed by a partial or excessive relapse as the treatment progressed. Only the patient on the 100 mg dose of TP-5 exhibited a continuous clinical deterioration of her condition. Thus, TP-5 obviously exerts some influence on the skin lesions of cutaneous T-cell lymphomas.

At present, a non-neoplastic etiology of mycosis fungoides is under discussion, interpreting the disorder as a misled continuous reaction to an unknown persistent antigen which finally deviates to malignancy (12, 13, 14). According to this view an immunoregulatory agent capable of disrupting this process would be of great value, theoretically and practically. It can only be speculated whether the changes in skin involvement observed during treatment in our patients are attributable to such a specific mechanism of action or

to simple interference with the inflammatory response, which seems possible in either direction via the reported effects of TP-5 or thymopoietin, respectively, on T-cells (3, 5, 6, 7, 8, 9, 10). Thus, flare-up reaction and clinical impairment as well do not necessarily indicate a true deterioration of the disease process, as only the reactive, possibly even beneficial inflammatory process may have been stimulated. On the other hand, short-term clinical amelioration must not be taken without reservation for an actual betterment as long as knowledge concerning the mechanism of this influence is lacking. With regard to the interpretation of the clinical effect, these considerations appear pertinent not only to mycosis fungoides, but also to the other T-cell lymphomas treated.

The increase in skin reactivity to recall antigens observed during application of TP-5 may be due to treatment, as a 'conversion of skin tests', probably attributable to the drug, has already been observed (10). It should be considered, however, that repeated testing itself has been found to enhance skin responsiveness to recall antigens (15). But as this could not be confirmed in another recent study (16), future evaluations on this account have to be awaited.

Further investigations, including double-blind studies, are clearly needed to determine the issue of treatment with TP-5 in cutaneous T-cell lymphoma, particularly mycosis fungoides. Especially the effect on histological and cytological features of the skin infiltrate and on the long-term course of the disorder should be elucidated. Before the application of TP-5 on a larger scale in cutaneous T-cell lymphomas is considered, it has to be clarified, at which stage of the disease it may be helpful, what dosage and mode of application should be chosen, and what combination with other therapeutic modalities are promising.

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