The Efficacy of Thymopentin Therapy for Prophylactic Use in Recurrent Herpes Simplex Virus Infection

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Background **: Herpes recurrences coincide with changes in the immunologic status of the patient, particularly in respect of cell mediated immunity (CMI), and it has been represented that thymopentin(TP) induces a wide range of immunoregulatory effects.**

Objective **: Relapses of herpes simplex seem to depend on the relationship between the cellular immune mechanisms and the virus in its latent phase, therefore immunomodulatory therapy may represent an alternative approach. In this respect, thymopentin may have the potential to become a valuable drug for prophylactic use in patients with recurrent herpes simplex.**

Methods **: Patients with moderate to severe herpes simplex(a relapse rate of at least 6 times/year) were treated with subcutaneous injection of thymopentin 50mg three times weekly for 6 consecutive weeks. The study consisted of a 6-week therapy and a subsequent 1 year follow-up on average.**

Results **: Fourteen of sixteen patients with herpes simplex improved as demonstrated by a reduction in the relapse rate, shorter duration of episodes and improvement in symptoms such as itching or pain. Four patients did not experience a relapse for more than 1 year after cessation of therapy. In this study, the duration of the symptom-free period increased and the average number of relapses per year was reduced.**

Conclusion **: Thymopentin is a highly effective drug, capable of positively influencing recurrent herpetic episodes and reducing the relapse rate.**

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Key Words: Herpes simplex, Thymopentin

Herpes simplex virus (HSV) infections belong to the most common viral diseases worldwide. After a primary infection, the HSV remains in the organism of the host in a latent or repressed state in neural gaglion cells[1]. Various stimuli such as exposure to a common cold, fever, sun and menstruation can trigger the transformation of the virus from the latent to the active stage, resulting in viral replication and the redevelopement of herpetic lesions[1]. In a minority of subjects, these relapses occur very frequently(one or even two relapses per month)[1]. For these patients with frequent recurrences, prevention of such relapses would be extremely important.

Many antiviral agents have been investigated in attempts to control or eradicate HSV disease. Although acyclovir is the present drug of choice for treating HSV infections, some adverse effects have been observed and acyclovir resistant HSV mutants have been isolated. Acyclovir does not appear to eliminate the latent virus in nerve ganglia since the infection may recur after treatment[1,2].

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The appearance of recurrent diseases seems to be influenced by the immune state of the host[1-3]. Thymopentin influences the differentiation of thymocytes and the function of mature T-cells[4,5]. By acting specifically on T-cells, it has been reported that thymopentin induces myriad immunoregulatory effects and provides clinical benefits for a number of chronic or recurrent infectons[4-8]. Based on these findings, we studied the effect of thymopentin on recurrent HSV infection.

PATIENTS AND METHODS

Study population: Between April 1990 and June 1992, patients visiting the Catholic University Medical College, Kangnam St. Mary's hospital, Seoul, were enrolled into the study with their consent. At the initial visit, patients were selected with a history of relatively frequent recurrences(> 6 relapses/year) and with a prior episode of treatment resistant HSV infections. Standard exclusion criteria included children under 10 years of age, pregnant women, concomitant other infections or significant disease, treatment with other antivirals. A diagnosis of recurrent HSV infections was initially made on the basis of history and clinical evaluation, and was subsequently confirmed by Tzanck test. Certain demographic characteristics of the patient population are summarized in Table 1.

Study design: This study was orginally planned as a six-week treatment period with subcutaneous injections of thymopentin 50 mg three times weekly for 6 consecutive weeks and for an additional follow-up of 1 year. The study was performed as an open trial. At the initial visit, a standardized medical history(duration of disease with frequent relapses, frequency of relapses in the last year, average duration of relapses in the last year, judgement of the severity of the disease, localization, etc) was obtained, and baseline laboratory tests(complete blood count, routine blood chemistry with renal function test, liver function test and urinalysis) were performed. After 6 weeks treatment, bimonthly and at the end of the follow up period the several parameters(number of relapses per year, duration of symptoms, symptom severity) were reassessed, and then the clinical effect and safety were judged. At the end of the study, the patients were asked whether or not they believed that their treatment had been useful. The frequency, duration and symptom severity of relapses before, during and after treatment are compiled for each individual represented in Table 3. At least 50% reduction in the relapse rate after therapy, shorter episodes of relapse duration and improvement of symptoms were defined "definitely improved"

Table 1. Characteristics of patients(n=16)

Sex distribution	M:F=10:6
Mean age(years)	47
range	10-61
Mean duration of herpes simplex before treatment(years)	4.9
range	1-18
Relapse rate/year	
<12	7
12-15	4
16-20	2
more than 20	3
Mean duration of symptoms(days)	12
range	5-30

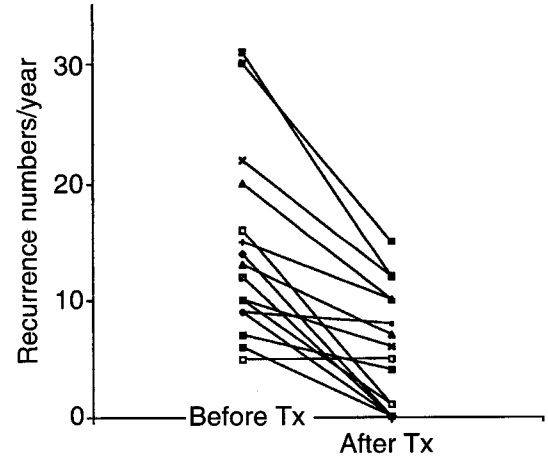

Fig. 1. Comparison of relapse rate($P<0.05$) before vs after treatment.
Tx: Treatment

RESULTS

The global therapeutic outcome of the study is

Table 2. Clinical effect of thymopentin against recurrent HSV(Patient profile)

Pt's Initial (No/Age/Sex)	Location	Recurrence/year (before/after)	Symptom severity* (before/after)	Duration of vesicles /day(before/after)	Assessment+ (Patient/Investigator)
KJT (1/50/M)	pubic area	12/0	2/0	7/3	excellent/excellent
LSC (2/38/M)	penis	9/0	2/0	6/0	excellent/excellent
KJS (3/35/F)	pubic area	6/0	3/0	5/0	excellent/excellent
HMR (4/10/F)	lip	14/0	3/1	5/0	excellent/excellent
YJW (5/56/M)	penis, buttock	10/1	2/2	7/4	marked/marked
LNW (6/53/F)	buttock	16/1	3/1	7/5	marked/marked
SJS (7/41/M)	pubic area	13/7	3/1	10/5	marked/marked
LEJ (8/58/M)	penis	20/10	3/1	9/4	marked/marked
KHR (9/61/M)	penis	31/12	3/2	7/4	marked/moderate
SHS (10/46/M)	penis, groin	15/10	3/1	7/3	moderate/moderate
KBJ (11/51/F)	sole(left)	30/15	3/2	26/10	moderate/moderate
LSJ (12/41/F)	vagina	22/12	3/2	8/5	moderate/moderate
CSN (13/40/F)	pubic area	10/6	3/1	7/3	moderate/moderate
OSW (14/57/M)	pubic area	7/4	3/1	8/5	moderate/moderate
KSY (15/42/M)	buttock	9/8	3/2	8/5	mild/mild
KCK (16/33/M)	lip	5/5	3/3	15/15	fail/fail

*Symptom severity(pain, itching, discomfort): 3; severe
2; moderate
1; mild(only erythema)
0; no symptom

+Assessment: excellent; no relapse
marked improvement; decrease in the relapse rate of at least 50%, shorter duration and improvement of symptoms
moderate; decrease less than 50%, shorter duraion and improvement of symptoms
mild; no decrement of relapse rate, shorter duration and improvement of symptoms

Table 3. Clinical observations in 16 cases of frequently recurring herpes simplex infection

Parameters	Before therapy mean/median (range)	After therapy mean/median (range)	Difference before/after mean/median (range)
Number of recurrences per year	14.3/14 (5-30)	8.6/6 (0-15)	5.7*/8 (5-15)
Average duration of recurrences(days)	8.9/7 (5-26)	4.3/4 (0-15)	4.6*/3 (5-11)
Symptom severity	2.8/3 (2-3)	1.5/1 (0-3)	1.3*/2 (0-3)

*Statistically significant($p<0.05$)

Table 4. Distribution of the investigator and patient's appreciation of the treatment

Assessment	Number and percentage of patients(total N=16)									
	Fail		Mild improvement		Moderate improvement		Marked improvement		Excellent	
	n	%	n	%	n	%	n	%	n	%
Patient	1	6	1	6	5	31	5	31	4	25
Investigator	1	6	1	6	6	38	4	25	4	25

compiled in Table 2. As can be seen, thymopentin induced significant improvement in recurrent herpes patients. According to the evaluation criteria, 8 out of 16 patients showed definitive therapeutic success with thymopentin treatment. Furthermore, four patients did not have a relapse during follow up period. Failure were registered only in one case.

During the follow-up period, comparing the anamnestic data before treatment with the observed ones after treatment, thymopentin provided significant improvement in the three parameters(Table 3). The number of relapses per year were reduced from 14.3 to 8.6 days on average, the average duration of recurrences decreased from 8.9 to 4.3 days and symptom severity dropped from 2.8 to 1.5, respectively. The relapse rate of each of the patients is shown in figure 1 at the end of the follow-up period.

In Table 4, appreciation of the investigators and patients on the treatment is analyzed seperately for thymopentin at the end of the study. The investigator's global evaluation corresponded rather closely with that of the patients.

There were no serious adverse experiences in thymopentin treated patient. Three patients experienced pain or itching sensation at the injection sites, lasting up to 30 minutes but generally lessening later in the trial. One patient experienced mild nausea after injection of 10 to 20 minutes duration. No other adverse experience was observed.

DISCUSSION

Infection with herpes simplex virus often results in a latent infection of local sensory ganglia characterized by periodic viral reactivation and mucocutaneous lesions[1-3]. The pathogenesis of herpes recurrence can be divided into separate phases: activation of latent HSV genome, centrifugal spreading of the virus via neurones, peripheral replication causing the local symptoms, and finally healing of the lesion most likely by the local host defence functions[1-3]. Latency appears to be lifelong but is periodically interrupted by virus reactivation, leading to apparent infections[3]. Most likely, host immune responses dictate the pattern of recurrences rather than the nature and quantity of latently infected neurons[3].

A series of factors has been associated with recurrence, including a wide range of emotional and physical stresses. These "trigger factors" are presumed to operate via common cellular, humoral, or deregulation of immune surveillance mechanisms required to contain the spontaneously reactivating virus[3,8]. However, the importance of antibodies in resolving the infection is unclear for several reasons. First, by spreading directly from cell to cell, herpes simplex virus may avoid potential neutralization or opsonization by antibodies. Second, agammaglobulinemic persons are not predisposed to more frequent or severe HSV infection. Third, specific antibodies do not protect against recurrent infection or neonatal herpes[9,10]. Thus it has been represented that cell mediated immune mechanisms are of paramount importance for the control of herpes simplex[8]. Many studies have verified the emergence of blastogenic responses, antibody monuclear cell populations in patients with primary or recurrent HSV infections[3]. Recent reports have documented spontaneous fluctuations in levels of leukocyte migration inhibitory factors and immune interferon during cycles of recurrences, but the pathogenic importance of these observations is still unclear[11].

Up to date, two basic approaches are ideally considered for the management of HSV infections[12]. The first is a vaccine to prevent the establishment of the latent infection, but no effective vaccines are yet available for herpes virus infections[13,14]. The second candidate is antiviral agents to

Table 5. Treatment of herpes simplex infection

a. Palliative and supportive care
pain, pruritus, fever, malaise or dehydration management and prevent bacterial infection
b. Unorthodox treatment
ascorbic acid, ether and surfactants, L-lysine monohydrochloride, cimetidine, cyclooxygenase inhibitors
c. Vaccines and immune stimulators
anti-HSV-1 glycoprotein D(gD), Levamisole, Interferon, Thymopentin
d. Antiviral agents
Acyclovir, Ganciclovir, Vidarabine, Foscarnet, Zidovudine, 2-deoxyglucose, Ribavirin

treat the infection once it is established. At this point, acyclovir remains the treatment of choice for HSV infections, but it does not appear to influence the frequency of disease reactivation among patients with very frequent recurrence[15].

Selective use of the drug should be advocated until further data are available on the drug's long term toxicity, and the possibility of resistant strains emerging[16]. Long term suppressive therapy with acyclovir does not eliminate ganglionic latency and reactivation of disease occurs after therapy is discontinued[3,15]. Other various therapeutic agents are currently used for the treatment of herpes but these only give symptomatic relief and they do not eliminate the virus from the host's body or reduce the frequency of reactivation(Table 5)[1-3].

Our study shows a third approach which may be applicable to patients suffering from frequent recurrences who can modulate the host immune status against viral infection. Thymopentin influences the immune system by promoting the differentiation of thymocytes and, perhaps more importantly, by affecting the function of mature T-cells[7]. Because recurrent HSV infections are related to the cellular immune status of the host(temporary deficit in CMI to HSV allowing a recurrence to become a clinical recrudescence), thymopoietin can be used as a prophylactic therapy in patients with recurrent HSV infection[4,17,18].

Three studies to investigate the effect of thymopentin in severe recurrent herpes genitalis and labialis were carried out. An open pilot study of 27 patients with frequent relapses(at least once a month) showed a marked improvement in 22 cases in whom the relapse rate decreased by at least 50% compared to the rate before treatment[19,20]. Another double blind, placebo controlled study in 42 patients with similiar severe herpes genitalis showed a significant reduction in the number of relapses as well as in the total duration of symptoms per month[21]. Similar results were found in a grup of 36 patients with labial herpes infection[22]. The immunoreconstructive and immunomodulatory effects of thymopentin on experimental herpes infections provided another clue for the therapeutic effect of thymopentin on frequently recurring herpes infections in mice which cannot be controlled with any of the current therapeutic tools except continuous administration of acyclovir[23]. our study is comparable with the data from earlier studies on the effect of thymopentin in recurring herpes infections. The present trial did not include a placebo control group. But, considering the highly significant differences between before treatment and after treatment, such an interpretation as relevance to the conclusions. Comparison of the frequency of relapses during the follow-up period was used as convincing evidence that thymopentin not only provides symptomatic relief but also aids the disturbed immune status of the patient. In this study, the average number of relapses per year and the duration of herpetic symptoms were reduced. According to the results of this study, we conclude that treatment with thymopentin is safe and offers significant therapeutic promise for recurrent herpes simplex infection. Further work is needed to dissect the possible mechanisms of thymopentin that affect recurrent herpes infection.

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