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In Vitro Cell-Mediated Immune Reactions in Herpes Zoster Patients Treated with Cimetidine

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SUMMARY **In a double-blind placebo-control study the immunomodulating effect of cimetidine treatment for one week and placebo was investigated for cell-mediated immune reactions of 22 patients with herpes zoster (HZ). The mitogen induced leukocyte migration inhibition test (LMIT) and the *in vitro* proliferation of the patients' lymphocytes to exogenous IL-2 were used. Before any treatment, the mitogen induced leukocyte migration inhibition capacity (LMIC) of HZ patients was found to be significantly reduced ($p < 0.02$) as compared to healthy blood bank donors (controls). After one week, within the same treatment, the LMIC was significantly improved ($p < 0.01$). The patients' lymphoproliferative response to IL-2, before any treatment, was not significantly different from that of controls ($p > 0.05$). However, significantly higher values ($p < 0.001$) were found in patients tested 7 days after the disease onset as compared to those tested after 12 days. One-week cimetidine treatment significantly improved ($p < 0.05$) the lymphoproliferative response to IL-2 of initially low responders and had no effect on higher responder patients. In contrast to this, after one week of placebo treatment, a significant decrease in the patients' lymphoproliferative response to IL-2 could be observed as compared to patients' initial responses ($p < 0.05$) or to those of controls ($p < 0.05$). Although the number of cases is very small. The data suggest that after cimetidine treatment, as compared to placebo, healing from skin rash and pain was achieved in a significantly shorter time ($p < 0.01$).**

Cimetidine is an H-2 histamine receptor antagonist (H_2 blocker) and over the last decade the immunomodulating effects of cimetidine have been investigated in animals and humans both *in vitro* and *in vivo*.[1] Although the mechanisms for immunomodulation are not completely delineated, it is known that T-lymphocyte suppressor cells possess receptors for histamine, that histamine has a critical role as a suppressor in cellular immune reactions, and that cimetidine and other histamine receptor antagonists inhibit suppressor cell functions.[1,2] The immunomodulating effect of cimetidine in cancer immunology, chronic mucocutaneous candidiasis, and the stimulation of the immune reactivity to bacterial antigens has been studied by a number of investigators.[3-6] Cimetidine enhanced the natural killer cell activity in patients with ovarian carcinoma and chronic lymphocytic leukemia,[7,8] augmented T-cell responses to IL-2, mitogens and alloantigens in melanoma patients,[9] and increased the production of migration inhibitory factors.[10,11]

In past years clinical observations concerning the effect of cimetidine treatment in herpes simplex and in herpes zoster (HZ) have been reported.[12-16] In the majority of cases, however, the possible correlation between immune reactions and clinical results of cimetidine treatment in HZ were not investigated and mainly sporadic case reports on clinical improvements after cimetidine treatment in HZ were published.

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Herpes zoster often develops in immunosuppressed patients[16] and *in vitro* immunopotentiation with IL-2 was reported.[17] The present study investigated the possibility that the *in vitro* lymphoproliferation to exogenous IL-2 may be differently affected by treatment of HZ patients with cimetidine as compared to placebo. The correlation of the patients' lymphocyte *in vitro* response to IL-2 before treatment was analysed according to the time elapsed from the illness onset. Clinical improvement (healing of skin rash and pain) was examined. In addition to this the mitogen-induced leukocyte migration inhibition test (LMIT) was performed before and after specific treatment. The LMIT was found by various investigators as well as by us to be a sensible test for the detection of specific and nonspecific cell-mediated immunity in parasitic, mycotic and viral infections[18-22] and cimetidine was found to have an immunomodulating effect in the production of macrophage and leukocyte migration inhibition factors.[5,10,11] The purpose of the present study is to study the immunomodulating effect of cimetidine treatment in the patients with herpes zoster.

MATERIALS AND METHODS

Patients

Twenty-two HZ patients, 9 men and 13 women, were tested. Thirty-five healthy blood bank donors, sex- and age-matched, were used as controls. Data on localization of the rash, severity of the illness, time passed from onset (as presented by the patient at his first presentation to the hospital), specification of treatment and healing, according to cured rash and disappearance of pain 7 days after treatment, are summarized in Table 1. The illness was categorized as severe, moderate or mild, according to the surface of vesicular rash, the number of the vesicles, the pain severity (Table 1). None of the patients suffered from a malignant disease and none received antiviral treatment, steroids or immunoglobulins. Three of them suffered from diabetes. In a number of cases, pain anticipated the appearance of the rash. Physical examination and routine laboratory tests were performed before and after treatment with cimetidine or placebo. Treatment was performed in a double-blind-placebo-controlled trial, and patients were informed by a signed consent that they were participating in an experimental trial.

Cimetag 400 mg (Cimetidine-Teva Inc, Petah-Tiqva, Israel) or placebo were prescribed 3 times daily for one week. Experiments were performed twice: before any treatment and one week after treatment.

Leukocyte migration inhibition test (LMIT) to PHA

The method used was essentially based on the technique described by Sorborg and Bendixen[23]

Table 1. Patients with herpes zoster: clinical data.

Patient	Sex/age		Localization and stage of HZ	Days after onset before treatment	Healing after 7 days of Rash	Pain
			Treatment: Cimetidine			
1. L.E.	F/60	R*	ribs (Mo)**	14	-***	+***
2. M.M.	F/65	L*	chest (Mo)	9	-	+
3. B.A.	F/53	L	chest (Mo)	21	+	+
4. Y.T.	F/46	L	chest (Mo)	5	-	-
5. S.M.	F/74	L	thigh and buttock (S)**	5	-	+
6. A.Y.	F/32	R	flank (Mo)	7	-	-
7. B.E.	F/61	R	forearm (Mo)	4	-	+
8. A.K.	M/82	R	scalp (Mo)	14	-	+
9. I.A.	F/68	L	flank (Mi)**	7	-	-
10. C.S.	M/72	L	chest (Mi)	7	+	+
			Treatment: Placebo			
11. A.I.	M/53	L	thigh (Mi)	9	-	-
12. S.F.	F/76	L	lower abdomen and buttock (Mo)	6	+	+
13. R.F.	M/66	R	flank and abdoman (Mi)	14	-	-
14. K.S.	F/78	L	lower ribs (Mi)	14	-	-
15. A.N.	F/57	L	neck and face (Mo)	7	-	-
16. Y.I.	M/42	R	thigh (Mo)	9	-	-
17. M.Y.	M/40	L	chest and axilla (Mi)	3	+	+
18. A.O.	M/73	R	neck, forearm and shoulder (Mo)	10	-	-
19. A.P.	M/35	L	thigh (Mi)	2	+	+
20. S.Y.	M/68	L	thigh (Mo)	10	-	-
21. T.S.	M/76	R	arm (Mi)	5	+	+
22. S.R.	F/90	R	lower abdomen	4	+	+

*R = right; L = left; **Mo = moderate; S = severe; Mi = mild; ***+ = rash or pain still exists; - = no rash or pain.

and Rouveix *et al.*[20] Briefly, leukocytes and sera from the 22 patients and 35 controls were obtained from 15 ml heparinized and 5 ml non-heparinized blood samples, respectively. The leukocyte rich supernatant (70–75% polymorphs and the remainder monocytes and lymphocytes) was centrifuged (250 × g), and the pellet washed twice with phosphate buffered saline solution (PBS). Cells were suspended in a concentration of 7×10^6 leukocytes/ml in RPMI 1640 supplemented with glutamine, antibiotics and 10% pooled heat inactivated human serum (pooled from 5–6 healthy volunteers and stored frozen until use). Cells were drawn in 25 µl silicone sealed glass capillaries, centrifuged and the capillaries were cut below the cell-fluid interface. They were secured with silicone grease, placed in chambers filled with RPMI 1640 supplemented with glutamine, antibiotics, 10% pooled or autologous serum and 2 µg/ml purified PHA (Wellcome, UK), and incubated for 24 hours at 37°C in 5% CO_2 atmosphere. Control chambers were filled with the same medium without PHA. Experiments were performed in triplicates.

After incubation the image of migration was projected, outlined, cut and weighed. The migration index (MI) was expressed as a ratio between test and control areas.[11,20] Increased MI values are reflecting decreased LMIF production and vice versa decreased MI values reflect increased LMIF production.

$$MI = \frac{\text{mean weight of migration area with PHA}}{\text{mean weight of migration area without PHA}}$$

Lymphocyte response to exogenous IL-2

Twenty millilitres of heparinized blood was processed for lymphocyte separation by Ficoll-Hypaque (Lymphoprep-Nycomed Pharma, Norway). To express IL-2 receptors, lymphocytes from 18 patients and 26 controls were activated for 12 hours with 10 µg/ml concanavalin A (Con-A, Bio-Makor, Rehovot, Israel) in culture medium (CM) containing glutamine, antibiotics and 10% pooled human serum.[24,25] After 12 hours, cells were washed in PBS containing 0.15 M M-methyl -D manopyronoside (Sigma, St. Louis, USA) to block any possible residual mitogenic activity of Con-A. The cells were further cultured for 4 days in the presence of 10 U recombinant IL-2 (Genzyme, Boston, USA) in CM. Cultures were prepared in quadruplicates, in flat microplates well type (Falcon, Becton Dickinson and Co California, USA) at a concentration of 2×10^5 cells/well and pulsed on day 4 for 5 hours with 1 µCi ^{3}H-thymidine (Amersham, Buckinghamshire, England), then harvested with an automatic cell harvester (Dynatech Automash 2000, Germany) and assayed for radioactivity by liquid scintillation in a β-scintillation counter (Beckman). For each case, cultures in the presence or in the absence of IL-2 were prepared. Results were expressed as mean counts/minute (cpm) of IL-2 stimulated minus mean cpm of IL-2 unstimulated cultures.

RESULTS

Leukocyte migration inhibition test

In 22 untreated HZ patients, as compared to 35 controls, a significantly increased mean MI toward PHA could be observed in the presence of autologous as well as in pooled human serum ($p < 0.02$

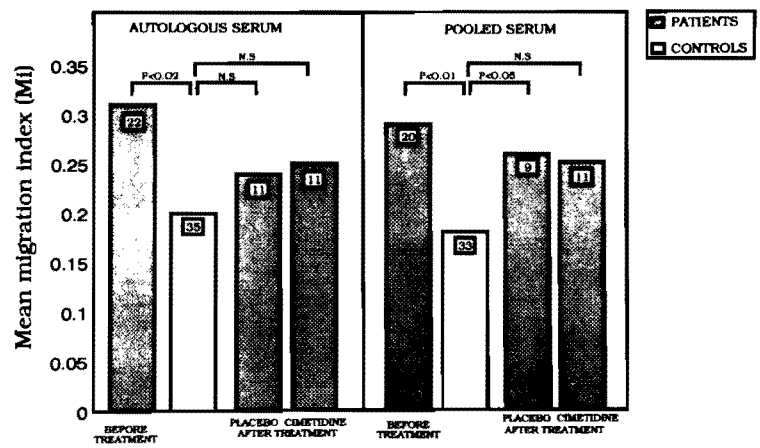

Fig. 1 Leukocyte migration inhibition test to PHA from 22 patients with herpes zoster. Data represent mean values of migration index (MI) from patients before and after treatment with cimetidine or placebo compared to 35 controls. Maximal deviation in multiple determinations were below 20%. In the presence of autologous as well as in pooled serum mean MI values from patients before any treatment were significantly higher than for controls ($p < 0.02$ and $p < 0.01$, respectively). The MI values decreased after one week in cimetidine and in placebo-treated patients and in the presence of autologous serum the difference between controls millilitres and treated patients was not significant ($p > 0.05$). In pooled serum, however, after placebo treatment MI values were still significantly higher as compared to controls ($p < 0.05$).

Table 2. Phytohemagglutinin induced leukocyte migration inhibition test in herpes zoster patients.

Treatment	Mean migration index ± SE*					
	Autologous serum			Pooled serum		
	Before Treatment	After Treatment	P**	Before Treatment	After Treatment	P
Cimetidine	0.32 ±0.06	0.25 ±0.04	NS	0.30 ±0.05	0.25 ±0.03	NS×
No. patients	11			9		
Placebo	0.29 ±0.04	0.24 ±0.03	NS	0.28 ±0.05	0.26 ±0.04	NS
No. patients	11			11		
Total (mean ±SE)	0.31 ±0.04	0.25 ±0.03	< 0.01	0.29 ±0.03	0.25 ±0.02	NS
No. patients	22			20		

*For details see Materials and Methods
**Students' t test for statistical analysis of differences
×NS = not significant

and $p < 0.01$, respectively, Fig. 1). One week later the same patients were tested again and an improvement in their LMIT, expressed by a decreased MI, could be observed in all patients: in those treated with cimetidine, as well as in those treated with placebo (Fig. 1 and Table 2). The differences, however, between MI values before and after treatment were significant ($p < 0.01$) when the test was performed in autologous serum, and was not significant ($p > 0.05$) for pooled serum (Table 2). In autologous serum MI values from patients one week after treatment were not significantly different from control values (Fig. 1). In pooled serum, however, a significant difference ($p < 0.05$) could still be found between controls and placebo treated patients (Fig. 1).

In vitro lymphocyte proliferation to exogenous IL-2.

The results for the whole group are summarized in Fig. 2. The immune *in vitro* response to IL-2 of previously activated patients' lymphocytes was not significantly different ($p > 0.05$) from that of 26 controls and the mean cpm values

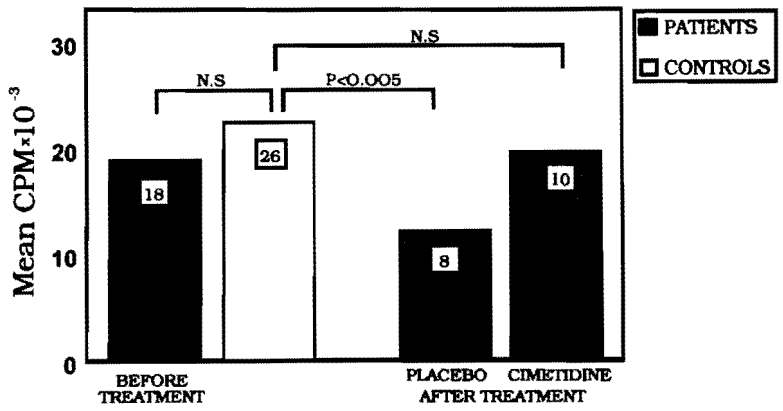

Fig. 2 The effect of exogenous IL-2 on the *in vitro* lymphocyte response of herpes zoster patients before and after treatment with cimetidine or placebo. Data represent mean count per minute (cpm) of ^{3}H-thymidine uptake from patients and controls. Maximal deviations in multiple determinations were below 20 %. Mean values from 18 patients before any treatment were not significantly different from those of 26 controls (18898 ±2861 cpm and 22518 ±3514, respectively). After one week the mean cpm values in 8 placebo treatment patients were significantly decreased as comapred to those of controls. In contrast to this, mean cpm from 10 cimetidine treatment patients were not significantly different from those of controls.

± SE were 18,898 ± 2,861 cpm and 22,518 ± 3,514 cpm, respectively (Fig. 2). The strength of the patients' lymphocyte responses to IL-2 before any treatment varied from case to case. When cases were divided in lower (below 14,000 cpm) and higher responders to IL-2 (above 14,000 cpm, Table 3), it was interesting to observe that the strength of the patients' lymphocyte response to IL-2 before any treatment seemed to be correlated to the time elapsed from the disease onset. Significantly higher responders were found between patients tested at a shorter time after the illness onset (mean 6.9 ± 0.8 days) as compared to low responders (lymphocytes from patients tested after a long time from the illness onset (mean 11.7 ± 2.1 days). The differences between high and low responders, as well as between the corresponding times of illness were statistically significant ($p < 0.0001$ and $p < 0.05$, respectively, Table 3). When the same patients were tested after one week of cimetidine or placebo treatment, the initial low responders receiving cimetidine were found to have a significantly increased ($p < 0.05$) response to IL-2 (Table 4). No significant difference ($p > 0.05$) between values obtained before or after cimetidine treatment could be observed in 4 high *in vitro* responders to IL-2 (Table 4). In contrast to this, in 8 placebo-treated patients (7 of whom were high responders) a significant decrease in the *in vitro* response to IL-2 could be observed after one-week treatment, and the difference between the first and the second test was statistically significant (19,967 ± 3,206 and 12,174 ± 2,964, respectively, $p < 0.05$, Table 4).

The healing process, as expressed by disappearance of skin rash and pain (Table 1), was correlated to specific treatment, to time elapsed from the illness onset, and to the patients' lymphocyte response to IL-2. For 3 patients healed after cimetidine treatment (Table 1,

Table3. Patients' *in vitro* lymphocyte response to IL-2, before treatment, correlated to time passed after disease onset.

Patients (number)	Mean cpm ± SE	Mean time passed after disease onset (days ± SE) before treatment
Low responders* (7)	8846 ± 1523	11.7 ± 2.1
High responders** (11)	25295 ± 3442	6.9 ± 0.8
P value***	< 0.001	< 0.05

* Patients with responses to IL-2 below 14000 cpm
** Patients with responses to IL-2 above 14000 cpm
*** Students' t test

Table 4. Effect of cimetidine or placebo treatment on patients' lymphocyte *in vitro* response to IL-2.

Patients (number)	Mean cpm ± SE Before Treatment	Mean cpm ± SE After Treatment	P value*
Cimetidine treated			
Low responders** (6)	8088 ± 1565	14480 ± 2858	< 0.05
High responders** (4)	32977 ± 7200	27464 ± 4731	NS
P value	< 0.01	< 0.05	
Placebo treated (8)v	19967 ± 3206	12174 ± 2964	< 0.05
Controls (35)vv	22518 ± 3514	22518 ± 3514	
P value+	NS	< 0.05x	

* Students' paired t test for differences
** For details see Table 3
v In placebo treated patients we had only 1 out of 8 low responders (13393 ± 200 cpm)
vv Control values were significantly higher as compared to low responders before treatment (8088 ± 1565 vs 22518 ± 3514, $p < 0.001$). They were not significantly different from low responders after cimetidine treatment, or from those of 4 high responders before or after treatment.
\+ Students' t test
x P value for placebo treated patients *vs* controls (12174 ± 2964 cpm and 22518 ± 3514 cpm, respectively.

Table 5. Time of healing (for skin rash and pain) and the *in vitro* response to IL-2 after cimetidine or placebo treatment.

Treatment	Mean time* of healing (days ± SE)	Response to IL-2 (mean cpm ± SE)		P value**
		Before Treatment	After Treatment	
Cimetidine (3)v	13.3 ±0.6	12410 ±4927	16391 ±3538	NS
Placebo (7)	17.4 ±1.0	19489 ±3617	11523 ±3324	NS
P value vv	< 0.01	NS	NS	

* Time after onset + time of treatment
** Students' paired t test for differences
v Number of healed patients (see Table 1)
vv Students' t test

cases 4,6,9), the duration of the illness was significantly shorter (mean time 13.3 ± 0.6 days), as compared to 7 healed patients treated with placebo (17.4 ± 1 days, $p < 0.01$, Table 5). In cimetidine treated healed patients, the mean value for IL-2 stimulated lymphocyte cultures was 25% higher than that before treatment ($p > 0.05$ not significant). In contrast to this, the mean value for IL-2 stimulated cultures from placebo-treated healed patients was 40% decreased as compared to mean values before treatment ($p > 0.05$, Table 5).

DISCUSSION

In HZ, like in other members of the herpes virus family patients, depressed cell-mediated immunity was often observed.[26-29] Impaired T-lymphocyte subsets were observed as compared to controls in HZ patients.[26] A slightly increased percentage of CD_4 lymphocytes, an increase in CD_8 (suppressor/cytotoxic) T lymphocytes and markedly decreased CD_4/CD_8 ratios were correlated to duration of acute herpetic pain.

Similar to other herpes produced diseases,[29] the significantly increased MI observed in this study in HZ patients, at their first presentation, as compared to controls, suggest a decreased mitogen-induced production of LMIF in the presence of autologous as well as in control serum. One possible explanation for the reduced production of LMIF may be the effect of suppressor cells on the production of this factor. Although antigen stimulated CD_4 and CD_8 amplification of lymphokine production was especially observed with the CD_4 helper subset[30] and not with T suppressor cells. The number of suppressor cells was not established in this study. However, an increased number of T suppressor cells was observed in HZ patients in the active stage of the disease.[27] Concomitant with an increased number of suppressor cells an increase in H-2 histamine receptor bearing suppressor cells may occur and affect the production of LMIF.[2]

Cimetidine treatment for one week had no specific effect on the mitogen stimulated LMIT from HZ patients. However, in both groups of cases, cimetidine and placebo treated patients, after one week, significantly improved MI values, reflecting an increased production of LMIF, were found. It may be that a time-correlated decrease in suppressor cells,[27] and an increased production of LMIF by the stimulated lymphocytes were effective in allowing the expression of MI values similar to those of controls.

In contrast to migration inhibition factors which were found to be inhibited by suppressor cells bearing H-2 histamine receptors,[2] no such effect was reported for IL-2 cell surface receptors.[31]

Our results on a decreased LMIF production and a normal proliferative *in vitro* response to IL-2 in HZ patients before any therapy, are in agreement with these findings. Although the number of cases is small, our results suggest that the immunorestorating effect of one-week cimetidine treatment, as measured by the proliferative *in vitro* response to IL-2, was effective for HZ patients with initially lower

response, as compared to higher responders. Higher proliferative responses were found in patients after a significantly shorter time after the illness onset, as compared to patients with lower initial responses. One possible explanation for the different effect of cimetidine treatment may be the time-correlated decrease of suppressor cells including H-2 histamine receptor bearing cells.[27] Patients treated with cimetidine 12 days after the illness onset may have a reduced number of suppressor cells bearing H-2 histamine receptors, as compared to those treated 7 days after the illness onset.[27] Cimetidine blockage of a reduced number of H-2 histamine receptors may be more effective and may finally lead to a greater availability of biologically active IL-2. receptors and a better *in vitro* proliferative response to exogenous IL-2 Similar to our results, in melanoma patients, a significant augmentation of T-cell responses to IL-2 after *in vitro* preincubation with cimetidine was reported for patients with initial relatively lower responses.[9] An *in vitro* synergistic tumor inhibiting effect of IL-2 and cimetidine against syngeneic murine tumors was found by Nakajima *et al.*[32].

In contrast to patients treated with cimetidine, in the placebo group, a decreased *in vitro* response to exogenous IL-2, as compared to controls, or to responses before treatment could be observed. It may be that the decreased *in vitro* response to IL-2 in one-week placebo treated patients is a time correlated effect. Before treatment 7 out of 8 patients in this group were high responders (Table 4). As a decline in the response to IL-2 could be observed in untreated patients as time increased (Table 3), this could be one possible explanation for the decreased *in vitro* response to IL-2 in the placebo group. In contrast, although the group is small, one-week cimetidine treatment did not decrease the initial *in vitro* high response to IL-2 of 4 HZ patients (Table 4). In low responders cimetidine enhanced the *in vitro* proliferative response of lymphocytes from HZ patients to exogenous IL-2. When the clinical effect of cimetidine and placebo were correlated to the time elapsed from the illness onset, although the number of patients is small, healing (as expressed by rash and pain disappearance) was achieved in a significantly shorter time after cimetidine, as compared to placebo treatment.

In further studies on HZ patients additional cell-mediated immune reactions and cell surface markers, as well as the effect of different cimetidine doses prescribed at specific times after illness onset, will be investigated.

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