Lactobacilli lozenges in the management of oral ulcers of Behçet's syndrome

L. Tasli[1], C. Mat[2], C. De Simone[3], H. Yazici[4]

[1]Fellow of Department of Dermatology, MD; [2]Professor of Department of Dermatology, MD, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey; [3]Professor of Department of Experimental Medicine, MD, University of L'Aquila, Rome, Italy; [4]Professor of Department of Medicine, MD, Division of Rheumatology, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey.

Please address correspondence to: Prof. Cem Mat, MD, Cerrahpasa Medical Faculty, Dermatology Department, Istanbul University, Aksaray, Istanbul, Turkey.
E-mail: cemmat@superonline.com

Received on September 5, 2005; accepted in revised form on June 1, 2006.

Clin Exp Rheumatol 2006; 24 (Suppl. 42): S83-S86.

Key words: Behçet syndrome, *Lactobacillus brevis*, oral ulcers.

ABSTRACT

Background. *There is increasing evidence that* lactobacilli, *having anti-inflammatory activity, may be useful in some diseases, particularly in inflammatory bowel disease.*

Objectives. *We aimed to study the efficacy of* lactobacilli *lozenges (INER-SAN®, VSL Pharmaceuticals, USA) in the management of oral ulcers of Behçet's syndrome.*

Patients and methods. *Twenty-five patients were studied before, during and after* lactobacillus *use. All patients had mainly skin-mucosa involvement with fresh oral ulcers and none were using systemic immunosuppressives. The patients chewed on 6 lozenges/day at intervals of 2-3 hours during the time they were awake for 7 days. The number of OU before visit 1 and after 1. and 2. weeks after drug use was the main outcome measure.*

Results. *Twenty three patients completed the trial. 1 patient left the trial the second day because of nausea and another was a no show at the 2.visit. There was a significant decrease in the mean number of ulcers following treatment, more pronounced among the females, and this decrease continued at least for 1 week after the treatment was stopped. 4/23 patients had side effects with 3 complaining of nausea and 1 of abdominal fullness.*

Conclusions. *In this pilot and open study* Lactobacillus brevis *CD2 lozenges seemed to be effective in controlling the OU of BS. Randomized, controlled trials with this seemingly innocuous agent are now needed.*

Introduction

Being the most common manifestation of Behçet's Syndrome (BS) oral ulcers (OU) rarely cause serious morbidity. Nevertheless they can surely affect quality of life in many patients. While the OU of BS can often be controlled by local measures, many times systemic medications like azathioprine (1) and thalidomide (2) need to be used. On the other hand, especially in a patient with no important disease manifestation at any one time during the disease course other than the oral ulceration - a rather frequent clinical situation in endemic areas - a remedy without the potentially more serious side effects of the mentioned agents would surely be welcome.

There is increasing evidence that lactobacilli are able to exert anti-inflammatory action in various diseases, particularly in inflammatory bowel disease (3). A *lactobacillus* strain has been recently characterized (*Lactobacillus brevis* CD2, proprietary strain of VSL Pharmaceuticals, Inc, Fort Lauderdale, FL, USA), which is endowed with a high activity of arginine deaminase (4). This enzyme acts on arginine, converts it to ammonia and citrulline and thus downregulates its conversion to nitric oxide, a major endogenous pro-inflammatory mediator.

A PubMed search revealed that chewing *lactobacillus* lozenges had been reported as beneficial idiopathic recurrent oral ulceration (ROU) in 1965 (5). It was interesting to note that no further studies were done in the ensuing 40 years.

In this open and pilot study, we studied the efficacy of *lactobacilli* lozenges in the management of OU of BS.

Methods

We have tested the efficacy of *Lactobacillus brevis* CD2 lozenges (INER-SAN® VSL Pharmaceuticals Inc., Gaithersburg, MD, USA) in OU among 25 consecutive patients with BS, all attending the multidisciplinary BS outpatient clinic of Cerrahpasa Hospital of University of Istanbul. To facilitate the return visits, the patients were chosen among those living in Istanbul. All had

Table I. Demographic data of our patient population and the number of oral ulceration before treatment, at the end of the treatment and after one week of stopping the drug. OU: oral ulcers.

Patient	Sex	Age	1st visit No of OU	2nd visit No of OU	3rd visit No of OU
1	M	30	6	4	0
2	M	18	1	8	4
3	M	48	1	0	0
4	M	26	7	2	0
5	M	34	9	7	2
6	M	29	3	3	1
7	M	34	2	0	0
8	M	47	10	6	6
9	M	28	3	2	2
10	F	29	5	1	0
11	F	45	4	1	2
12	F	24	6	1	0
13	F	46	2	1	2
14	F	43	4	4	1
15	F	48	2	0	0
16	F	44	1	3	1
17	F	29	4	6	0
18	F	41	9	5	3
19	F	26	3	1	0
20	F	50	4	2	1
21	F	37	4	1	1
22	F	31	2	1	1
23	F	33	2	3	2
24*	M	28	6	8	6
25*	M	33	7	8	6
Mean (range) number of OU			4.6 (1-10)	3.1 (0-8) **	1.6 (0-6) ***

*: drop outs; scores replaced by the highest value otherwise observed among the same gender for that visit; ** p = 0. 023; *** p = 0. 0001.

mainly skin-mucosa involvement with OU, age ≥ 18, none was using systemic immunosuppressants, systemic antibiotic and topical medications. They were to be excluded from the study if such medication had to be started during the trial. The patients were informed about the possible side effects like nausea, vomiting and abdominal fullness.

The number of OU were counted immediately before (1st visit) and after 1 week's (2nd visit) lozenge use. The patients chewed 6 lozenges/day at intervals of 2-3 hours while they were awake for 7 days. All patients were also seen once more 1 week after completion of the study (3rd visit) and again the OU were counted.

In order to put our results in a better perspective, after the trial was finished and we analyzed our results, we also prospectively looked at the fate of OU ulcerations among a small group of 10 volunteer patients with BS with the same disease specifications at the time of entry into the formal study. These patients did not receive *lactobacillus* tablets but used local measures if needed. The study protocol was approved by the local ethics committee of the Cerrahpasa Hospital and all patients gave written informed consent .

Table II. Oral ulcers among the males and females tabulated separately.

	mean number of OU (range)			P*	
	1st visit	2nd visit	3rd visit	1st vs 3rd visit	1st vs 2nd visit
Males n:11	5.0 (1-10)	4.4 (0-8)	2.4 (0-8)	0.32	0.03
Females n:14	3.7 (1-9)	2.1 (0-6)	1.0 (0-3)4	0.003	0.001

* Wilcoxon signed rank test.

Results

Out of the 25 patients (11 males, 14 females, mean age 35.2 ± 8.9 SD years), 23 (9 male, 14 female) completed the trial. Two male patients could not complete the study. First patient left the trial on the second day because of nausea and another patient was a no show at the 2nd visit. Four out of 23 patients had side effects. Three patients complained of nausea and 1 patient of abdominal fullness.

Table I shows the number of OU, all minor ulcers (6), counted at each visit in each patient. An analysis by the Wilcoxon signed ranks test showed that there was a significant decrease in the number of oral ulcers both at the end of the 1st week (p = 0.023) and at the end of the 2nd week (p = 0.001). In this intention to treat analysis, the greatest number of ulcers observed among the patients still in the trial for visit among the patients of same gender, was assigned to the missing ulcers in the 2 drop-outs (patients 24 and 25). Separate analyses for males and females, again with the Wilcoxon signed rank tests, showed that this decrease was more pronounced among the females (Table II).

Discussion

In this pilot study *Lactobacillus brevis* CD2 lozenges seemed to be rather effective in controlling the OU of BS. Similar to our previous experience with colchicine (14), depot-steroids(21), females showed more tendency for improvement with this agent, as well perhaps reflecting more resistant disease among the males, in general among the Behçet patients (8-11). We need to underline however this was an open study among a limited number of patients and, as in any uncontrolled study, the biases, such as the regression to the mean effect, could have affected our results.

Table III. The number of ulcers in individual patients in BS patients who did not receive losenges at the beginning, one week and two week later.

Patient number	Sex	Number of OU 1st visit	2nd visit	3rd visit
1	M	1	1	1
2	M	3	4	5
3	M	1	1	1
4	F	3	3	3
5	F	2	1	2
6	M	2	1	2
7	M	2	1	2
8	F	2	4	4
9	F	3	3	1
10	M	2	0	1
Mean number of OU		2.1	1.9	2.2

The number of ulcers in individual patients in the post study control group is given in Table III. The trend observed in the formal study group was not present here and this, we believe, gives more weight to our favorable findings in the formal study. On the other hand, comparing Tables I and III, the baseline numbers for the oral ulcers were higher in the post study control group, pointing to a regression to the mean bias. However a formal regression to the mean analysis (7) revealed that a substantial regression to the mean (0.37%) was also present in the control group, being 0.54% in the study group. Furthermore the still lower mean value of oral ulcers at week 2 – one week after stopping the lozenges – suggests that the observed lowering of the oral ulcers was probably real. Nevertheless these considerations can only be clarified with a proper, randomized controlled trial.

Many of our patients reported subjective relief from ulcer discomfort within a few days of the lozenge use. This certainly is in line with the, admittedly rather informal observations of Rapoport and Levine (5) in their patients with ROU in their. It is interesting to note that thalidomide, another agent rather useful agent in ROU also works in OU of BS (2), perhaps suggesting a common disease mechanism.

Topical steroids which adhere oral mucosa (triamcinolon acetinoid 0.1%) usually shorten duration of oral ulcers and topical anesthetics (lignocaine gel 2%) may help pain control (12). Topical sucralphate suspensions has also been found to be effective in oral ulcers in a double blind study(13). Topical interferon alfa 2a (14), topical cyclosporine A (15), topical chromolyn gel 4% (16) found ineffective in placebo controlled double-blind studies.

Apart from those local agents many systemic drugs such as thalidomide (17), colchicine (18), dapsone (19), various antibiotics [penicillin (20), azitromycin (21)], interferon alfa 2a (22-24), depot-steroids (25) has been investigated in the treatment of mucocutaneous lesions. Thalidomide, interferon alfa 2a, etanercept (26), dapsone, azathioprine (27), cyclosporine A (12) are useful drugs for the treatment of mucocutaneous manifestations of BS.

It is to be underlined that all systemic remedies, as outlined above for OU have more or less some potential side effects. This makes the need for randomized, controlled trials with this seemingly innocuous treatment both in OU associated with BS and in ROU more pertinent.

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