

Frequent oral ulceration during early disease may predict a severe disease course in males with Behçet's syndrome

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ABSTRACT

Objective. The numbers and recurrence rates of mucocutaneous manifestations can be highly variable among patients with Behçet's syndrome (BS) but it is not known whether these differences influence the disease course at the long-term.

Methods. We evaluated the outcome of 30 patients that made up the placebo arm of a 6 months controlled trial of thalidomide and looked at the relation between the frequencies of mucocutaneous manifestations during the trial and the development of major organ involvement necessitating immunosuppressives during the post-trial period.

Results. Fifteen (50%) patients had received immunosuppressives for major organ involvement during the post-trial period. Patients receiving immunosuppressive treatment were significantly younger at the onset of BS compared to those who did not (24.5 ± 5 vs. 29.7 ± 3.8 SD years; $p=0.003$). The mean number of oral ulcers recorded throughout the trial was significantly higher among patients using immunosuppressives compared to those who did not (2.09 ± 0.96 vs. 1.43 ± 0.8 ; $p=0.029$). This significance disappeared when adjusted for age of onset of BS ($p=0.16$). ROC curve analysis showed that having 10 or more ulcers during 6 months has a sensitivity of 86.7% and a specificity of 53% for the subsequent necessity of immunosuppressive use. The same association was not true for genital ulcers, follicular lesions and erythema nodosum.

Conclusion. These findings on a limited number of patients suggest that frequent occurrence of oral ulceration during the initial years of the disease may predict the development of major organ involvement in men with BS.

Introduction

The clinical course of Behçet's syndrome (BS) can be highly variable due to the heterogeneous nature of organ

involvement and fluctuations in disease activity. For the majority of patients, BS is an annoying disease affecting quality of life with its recurrent mucocutaneous manifestations, while others may develop serious disease in the eye, major blood vessels or central nervous system involvement resulting in significant disability and mortality (1, 2).

Immunosuppressives are the mainstay of treatment in BS. Their use in early disease might be helpful in preventing the development of major organ involvement (3). However, long-term treatment with immunosuppressive drugs carries the risk of significant adverse events and recognising patients who in time will develop more severe disease is essential. It has been known for a long time that the disease runs a more severe course among young men but the conditions for development of major organ involvement even in these patients have not been adequately elucidated (4).

Mucocutaneous manifestations are the most frequent symptoms of BS. Their numbers and recurrence rates can be highly variable between patients but it is not known whether these differences influence the disease course of BS. A recent outcome study from Japan could not find a relation between the initial clinical manifestations of the patients and the later development of organ involvement (5). We had also reported that male BS patients could still have a serious disease course even when they were free of major organ involvement during the early years of the disease (6).

In this study we evaluated the long-term outcome of a homogeneous group of male BS patients who made up the placebo arm of a controlled trial during the early years of their disease (6, 7). This allowed us to assess any relation between the natural course of mucocutaneous lesions during the trial and the outcome. We hypothesised that patients with more frequent mucocutane-

Competing interests: none declared.

ous manifestations early in the disease course would also have more serious disease later on.

Methods

The efficacy of thalidomide in suppressing the mucocutaneous manifestations of BS was shown in a double blind, placebo controlled trial that was conducted between October 1993 and November 1996 (7). The patients in this trial were all male, were aged between 18 and 35 years and had a mean disease duration of 2.8 years. They all had active mucocutaneous disease but no other organ involvement.

From October 2006 to March 2007 – a mean of 11.7 years after the trial had ended – we surveyed these patients for the development of major organ disease requiring immunosuppressives during the post-trial period (6). Thirty-nine patients (43%) had used these drugs. Being young at the onset of BS (under 25 years of age) was the strongest risk factor for developing organ involvement, whereas being allocated to thalidomide during the trial had no impact on the outcome. In the current study we evaluated only those patients who made up the placebo arm of the thalidomide trial for the use of immunosuppressives during the post-trial period (7). Throughout the trial these patients were examined every 4 weeks and the numbers of new mucocutaneous lesions (oral ulcers, genital ulcers, erythema nodosum) were recorded. Follicular lesions were assessed according to a scoring system (no lesions = 0; 1–5 lesions=3; 6–15 lesions=10; and more than 15 lesions=16). The first visit (week 0) was the first day of the trial before the patients took the medications (placebo tablets) and the last visit was done 4 weeks after the trial had ended (week 28). The study cohort consisted of 30 patients who have completed the trial (out of a total of 32) and who have been re-evaluated later.

Statistical analysis

Student's *t*-test, Fisher exact test and Mann-Whitney U-test were used for comparison of the patient groups regarding the use of immunosuppressives. Chi-Square Fisher exact test was used for adjustment of the effect of age

Table I. The demographic findings of patients with regard to the use of immunosuppressive treatment.

	Age at onset (mean ± SD) years	Number (%) of patients with young age at onset	Disease duration at the entry to thalidomide trial (mean ± SD) years	Time to initiation of immunosuppressives (mean ± SD) months
Received immunosuppressives (n=15)	24.5 ± 5.7	(47%)	2.6 ± 1.3	24.6 ± 23.3
Did not receive immunosuppressives (n=15)	29.7 ± 3.82	(13%)	2.8 ± 1.6	–
<i>p</i> -value	0.003	0.101	0.67	

Table II. The frequencies of mucocutaneous lesions (mean ± SD) recorded during the trial with regard to the later use of immunosuppressives.

Patients (n=30)	Oral ulcers	Genital ulcers	Folliculitis	Erythema nodosum
Received immunosuppressives (n=15)	2.09 ± 0.96	0.38 ± 0.46	7.17 ± 2.96	0.21 ± 0.37
Did not receive immunosuppressives (n=15)	1.43 ± 0.8	0.44 ± 0.5	5.88 ± 4.26	0.29 ± 0.93
<i>p</i> -value	0.029	0.45	0.245	0.61

at onset on the distribution of oral ulcer frequency. Cut-off point, sensitivity and specificity of the total number of oral ulcers for predicting immunosuppressive use were made with receiver operating characteristics (ROC) curve method. The ethics committee of Cerrahpasa Medical Faculty has approved the thalidomide trial and the post-trial outcome survey.

Results

Fifteen of the 30 patients (50%) had to use immunosuppressives (eye involvement=10 patients, vascular involvement=2 patients, CNS involvement=2 patients, severe mucocutaneous involvement=1 patient) during the post-trial period. Patients receiving immunosuppressive treatment were significantly younger at the onset of BS than those who did not receive immunosuppressives (24.5±5.7 SD years vs. 29.7±3.8 SD years; *p*=0.003). The demographic findings of the patients are summarised in Table I. The mean numbers of mucocutaneous lesions recorded during the trial and their relation to the development of complications requiring the use of immunosuppressives during the post-trial

period are shown in Table II. Patients developing complications later on had significantly more frequent oral ulcers than those who did not (*p*=0.029). This significance, however, disappeared when adjusted for age at onset of BS (*p*=0.16). The mean numbers of genital ulcers, follicular lesions and erythema nodosum were similar between patients regarding the initiation of immunosuppressives. ROC curve analysis showed that having 10 or more oral ulcers during the 28 weeks had a sensitivity of 86.7% and a specificity of 53% for the later development of complications requiring immunosuppressive treatment (Fig. 1).

Discussion

This study, for the first time, suggests that frequent oral ulceration during early disease may be a risk factor for a more serious disease course in men with BS. Such a relationship could not be shown for the other types of mucocutaneous manifestations but this might be also due to their relatively low numbers at hand.

The patients in this study were part of our previous study, in which we had looked

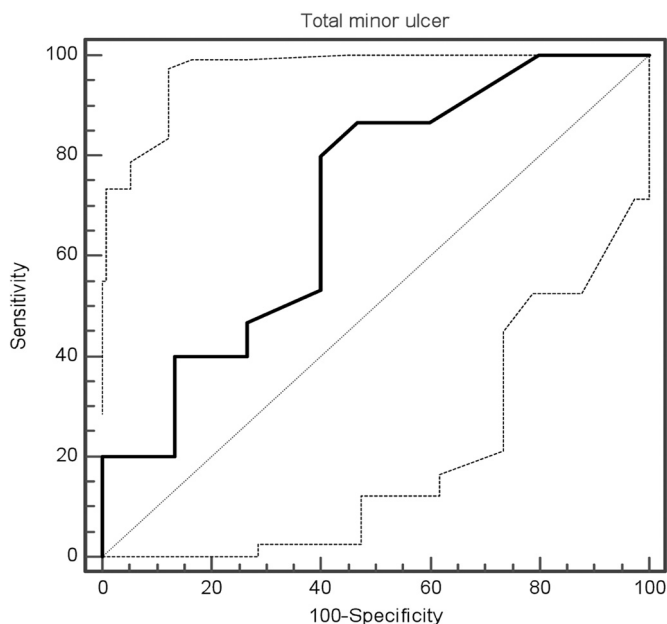


Fig. 1. ROC curve analysis: AUC=0.704, $p=0.036$. Cut-off for 10 or more total number of oral ulcers: Sensitivity=86.67% Specificity=53.3%

at the long-term outcome of all patients who had entered the thalidomide trial (6). The current study enables us to assess the natural course of mucocutaneous manifestations in patients allocated to placebo during early disease course and their correlation with outcome.

Recurrent oral ulceration is the most frequent symptom of BS. The International Study Group Classification Criteria require the presence of recurrent oral ulceration in all patients for the diagnosis of BS (8). It is the initial symptom in roughly 90% of the patients and can precede the diagnosis of BS for a mean of 7.5 years (5, 9). Mucocutaneous manifestations of BS disappear in the late stages of the disease but oral ulcers continue to appear as recently shown in a study in 60% of the patients after 30 years of disease onset (10). These observations suggest that recurrent oral ulceration has an intrinsic role in the pathogenesis of BS. On the other hand, it is not easy to explain why frequent oral ulceration during early disease might be associated with a more severe disease course. It was shown that certain streptococcal strains are increased in the oral flora of BS patients suggesting the role of microorganisms in the pathogenesis of BS (11). Frequent oral ulceration may induce disruption of oral mucosa leading to the entrance of these microorganisms to the circulation.

The activity of oral ulceration is traditionally assessed with measures such as the size, number, recurrence rate and healing time of the ulcers (12). Two retrospective studies reported a higher frequency of major oral ulceration (ulcers larger than 1 cm in diameter) among BS patients compared to patients with idiopathic oral ulceration (13, 14). Patients with major oral ulcers had significantly more frequent relapses and higher number of ulcers per episode compared but the size of ulcers had no influence on disease severity and systemic expression of BS. We had also assessed the size of oral ulcers in addition to their numbers but there were very few patients with major ulcers preventing a realistic assessment.

In the previous survey 76% of patients developing BS at young age had experienced major complications at long-term compared to 30% of those developing BS at old age (6). These figures, at one hand, re-emphasise the risk of serious disease course for men but they also show that a considerable subset of these patients, even among the young aged, will preserve their mild disease course limited to mucocutaneous manifestations. Thus the frequent occurrence of oral ulceration during early disease may be a helpful clue for the clinician in predicting the disease course at long-term. We realise that our results are based on small numbers of patients and need

further validation. Nevertheless, future studies looking at predictors of severe disease course in BS should also take into account the frequency of oral ulceration.

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