Oral ulcer activity assessment with the composite index according to different treatment modalities in Behçet's syndrome: a multicentre study

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ABSTRACT

Objective. *The aim of this multicentre study was to understand patients' needs and to evaluate the oral ulcer activity with the Composite Index (CI), according to different treatment modalities in Behçet's syndrome (BS).*

Methods. *BS patients (n=834) from 12 centres participated in this cross-sectional study. Oral ulcer activity (active vs. inactive) and the CI (0: inactive vs. 1-10 points: active) were evaluated during the previous month. The effects of treatment protocols [non-immunosuppressive: non-IS vs. immunosuppressive: (ISs)], severity (mild vs. severe), disease duration (<5 years vs. ≥5 years) and smoking pattern (non-smoker vs. current smoker) were analysed for oral ulcer activity.*

Results. *Oral ulcer activity was observed in 65.1% of the group (n=543). In both genders, the activity was higher in mild disease course with non-IS treatment group compared to severe course with ISs ($p<0.05$). As a resistant group, patients with mild disease course whose mucocutaneous symptoms were unresponsive to non-IS medications were treated with ISs in a limited period and achieved the highest CI scores in females. Oral ulcer activity and poor CI score were associated with disease duration less than 5 years compared to others in male patients ($p<0.05$).*

Conclusion. *Oral ulcer activity pattern is affected by both the combination of disease course, treatment protocols and disease duration. CI scores reflected the oral clinical activity and CI might be a candidate scale to evaluate the efficacy of treatments during the follow-up of oral ulcer activity in BS.*

Introduction

As a chronic and relapsing systemic inflammatory disorder, Behçet's syndrome (BS) is characterised by oral, genital ulcers and cutaneous ocular, arthritic, vascular, central nervous system and gastrointestinal involvement. Oral/genital ulcers and cutaneous involvement such as mucocutaneous manifestations and musculoskeletal involvement form the milder clinical spectrum of the disease. In contrast, the severe course includes ocular, vascular, neurological and gastrointestinal manifestations with high risk for mortality and morbidity. Severe disease course and resistant mucocutaneous manifestations are treated with immunosuppressives (ISs: azathioprine, corticosteroids, anti-TNF-α agents and interferon-α), whereas non-IS medications (colchicine, salazopyrine, NSAIDs and antibiotics) could be used in mild disease course and during the remission phase of major organ involvement, especially in the older age group (1). Severe disease course is commonly observed in male BS patients, whereas females are usually in the mild disease spectrum (2). Neutrophils are implicated in the pathogenesis and activated by testosterone as the primary sex hormone in men. Male gender is thought to be a critical prognostic factor in BS (3-7).

Clinical presentations are key assessment tools as specific laboratory tests are not available for disease monitoring in BS. Oral ulcers are considered to be a diagnostic hallmark in the internationally accepted criteria (8). In clinical practice, they could be the first sign or the primary symptom of BS. Close as-

sociations are present between disease severity, treatment protocols and oral ulcer activity in BS patients (2). Topical medications are thought to be the first line of treatment for oral ulcers. Oral ulcer activity is commonly seen in patients with mild disease course and patients treated with non-IS medications (9). However, IS medications are used in a limited period in patients whose mucocutaneous manifestations are uncontrolled with non-IS medications. In addition, oral ulcer could be persistent, although manifestations regarding severe disease course are in remission (2, 10). While achievement of complete remission is an unrealistic target in clinical practice (2), oral ulcer activity of patients can be used to assess the disease activity and the efficacy of treatment protocols (11, 12).

Although a reliable tool for the assessment of oral ulcer activity is necessary, no consensus exists on the ideal method in BS. The number and healing time of oral ulcers are commonly evaluated in BS, however, pain and functional status that affects daily life are underestimated. The 'Composite Index' as a patient-reported outcome measure (PROM) is a validated oral ulcer activity index, developed by our study group, that evaluates pain and functional limitation due to oral ulcers and easily monitors oral ulcer activity in patients with BS (11, 12) and recurrent aphthous stomatitis (RAS) (11) (Fig. 1). No multicentre study focusing on oral ulcer activity and PROMs has been performed in BS. Therefore, the aim of the multicentre study was to evaluate oral ulcer activity and the "Composite Index (CI)" as an organ-specific oral ulcer activity index according to different treatment modalities in mild *versus* severe course in BS.

Materials and methods

In this cross-sectional study, 834 BS patients (F/M: 441/393, age: mean: 38.4±10.9 years) diagnosed by the International Study Group criteria (8) and followed in BS clinics from 12 centres were included. The data were collected through clinical examinations and a questionnaire regarding disease-related factors and smoking pattern from September 2017 to March 2018. A meeting with the study group was held to standardise data collection protocol before starting the study.

Clinical manifestations of BS patients were as follows: oral ulcers (n=834, 100%), genital ulcers (n=710, 85.1%), cutaneous (n=633, 75.9%), musculoskeletal (n=444, 53.2%), ocular (n=165, 19.8%), vascular (n=106, 12.7%), neurological (n=34, 4.1%) and gastrointestinal (n=13, 1.6%) involvement (Table I). Positive pathergy reaction was observed in 57.7% of the patients (n=481). The mean disease duration was 9.03±7.6 years in the study group. Disease duration was categorised estimating the early period of the disease as less than 5 years (n=334, 40.04%) *vs*. ≥5 years (n=484, 58.03) for the analysis. It was not determined in 16 patients (1.94%).

A disease severity score reflecting organ involvement was calculated in BS patients (13) and was found to be 4.5±1.9 in the group. The patients were then categorised as mild disease course with mucocutaneous manifestations and musculoskeletal involvement (n=582, 69.8%) and severe disease course with ocular, vascular, neurologic, and gastrointestinal involvement (n=252, 30.2%). They were treated with non-immunosuppressive (non-IS) medications regarding colchicine, salazopyrine, NSAIDs, antibiotics (n=501, 60.07%) or immunosuppressive medications (ISs; n=289, 34.65%), such as azathioprine, corticosteroids, anti-TNF-α and interferon-α in severe disease course. In addition, 44 patients were not taking any medication (Table I).

The primary objective of the study was to evaluate factors associated with oral ulcer activity in BS. During the clinical examination the patients were asked about the number and healing time of their oral ulcers in the previous month. Since oral ulcer activity could be affected by both disease severity (mild *vs*. severe) and treatment protocols (non-IS *vs*. ISs), they were combined to eliminate bias in the study. However, the 44 patients who were not taking any medications were not included in these subgroups. Oral ulcer activity was evaluated in these four subgroups: Group 1) mild disease course with non-IS medications (n=429; 51.4%); Group 2) mild disease course with IS medications (n=111; 13.3%); Group 3) severe disease course with non-IS medications (n=72, 8.6%) and Group 4) severe disease course with IS medications (n=178; 21.3%). (Table I).

Although IS medications were not the standard treatment protocol in the mild disease course, they were used in limited periods (0.7±0.6 years) to control mucocutaneous manifestations that were unresponsive to non-ISs in Group 2. Since there was evidence of remission of major organ involvement in this group, non-ISs were also used in Group 3. As predicted, the disease duration was longer in Group 3 (12.4±9.1 years) compared to the others (Group 1: 8.9±7.5, Group 2: 6.8±6.2, Group 4: 8.7±6.9 years) (p<0.05). Smoking habits of the group (n=812) were categorised as current smokers (n=216, 25.9%) and non-smokers that included past smokers/never smokers (n=596, 71.5%). Data were not available for the other 22 patients (2.6%).

Composite index as a patient-reported outcome measure

The presence of oral ulcers, as well as oral ulcer-related pain and functional disabilities were evaluated using the Composite Index (CI) as a secondary outcome of the study (11, 12) (Fig. 1). Since CI is an organ-specific patient-reported outcome measure, it assesses both pain and functional status such as chewing, speech and tasting, which are directly affected by oral ulcer activity. The patients filled in the index form during the clinical examination. The score of the CI ranged between 0 and 10 points; the presence of oral ulcer was coded as "0" for inactive and "1" for active.

- Oral ulcer-related pain was evaluated using a 100 mm-visual analogue scale (VAS; 0 = no pain, 100 = severe pain). The scores were presented as ≤10: 0; 11-20: 1; 21-40: 2; 41-60: 3; 61-80: 4; 81 and over: 5 points.
- The impact of oral ulcers on functional status was assessed by Likert type scale: (none of the time: 0 points, a little of the time: 1 point;

Table I. Clinical manifestations in patients with Behçet's syndrome.

Organ involvement	n	%
Oral ulcer	834	100
Genital ulcer	710	85.1
Cutaneous	633	75.9
Musculoskeletal	444	53.2
Ocular	165	19.8
Vascular	106	12.7
Neurological	34	4.1
Gastrointestinal	13	1.6
Disease course		
Mild (mucocutaneous manifestations and musculoskeletal involvement)	582	69.8
Severe (ocular, vascular, neurologic and gastrointestinal involvement)	252	30.2
Total	834	100
Current treatment modalities		
Non-IS: colchicine, salazopyrine, NSAID, antibiotics	501	60.07
IS: azathioprine, steroids, anti-TNF-α and interferon- α	289	34.65
No medication	44	5.27
Total	834	100
Disease course with treatment protocol		
Mild disease course with non-IS medications	429	51.4
Mild disease course with IS medications	111	13.3
Severe disease course with non-IS medications	72	8.6
Severe diseases course with IS medications	178	21.3

1. Oral ulcer activity: (0-1 points)

Number of oral ulcers during the last month: 0=0 point, ≥1= 1 point

2. Pain status: (0-5 points)

Please place a vertical mark on the scale below to describe how you felt pain due to your oral ulcer during the last month.

0 No pain — 100 Severe pain

3. Functional state: Please describe the effects of oral ulcers on your oral functions in the last month (0-4 points)

How often.....	None of the time (0)	Little of the time (1)	Some of the time (2)	Most of the time (3)	All of the time (4)
Did you feel unpleasant *taste* in your mouth due to oral ulcers?					
Did you have difficulty in *speaking* due to oral ulcers?					
Did you have difficulty in *eating/chewing/swallowing* due to oral ulcers?					

*Total score: 0-10

Fig. 1. Composite index for oral ulcer.

some of the time: 2 points; most of the time: 3 points; and all of the time: 4 points).

The inclusion criteria were: >18 years of age and being under medical control for BS. The presence of other chronic conditions leading to oral ulcers was an exclusion criterion.

The study was performed according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Marmara University Medical School (July 14 2017; no. 09.2017.497). Informed consent was obtained from all patients.

Statistical analysis

Analyses were carried out by using SPSS 16.0 statistical package programme (SPSS Inc, Chicago, IL, USA). Mann-Whitney U-test and Spearman correlation test were used because of the non-normal distribution of data in the study. In addition, chi-square test was used to compare the categorical data. Cronbach-alpha for internal reliability was found as 0.911 in the functional subscale of CI. A *p*-value ≤0.05 was accepted as statistically significant.

Results

Over half of the group (n=543; 65.1%) had active oral ulcers during the previous month. The number and healing time of oral ulcers were 2.9±2.7 and 7.1±4.1 days in the active group. The CI scores and the subscales of functional status and pain status as PROMs were 6.03±2.3, 1.9±1.2 and 3.1±1.4, respectively, in the active patients. The number and healing time of oral ulcers correlated with the CI scores (r: 0.40, p=0.000; r: 0,37, p=0.000), functional status (r: 0.38 p=0.000; r: 0.33, p=0.000) and pain level in the group (r: 0.32, p=0.000; r: 0.34, p=0.000).

The presence of oral ulcer activity was higher in females (56.9%) compared to males (43.1%) (p=0.002). Mean age, disease duration and disease severity score were lower in patients with active oral ulcers (37.1±10.4 years, 8.3±7.6 years and 4.2±1.7, respectively) compared to those of the inactive patients (40.7±11.3 years, 10.5±8.03 years, 4.9±2.2, respectively) (p=0.000 for all) (Table II).

The disease severity score that reflects organ involvement was significantly lower in female patients (4.2±1.8) than males (4.7±1.9) (p=0.000) and, as expected, IS use was higher in males (46% *vs*. 28% of females). Being a non-smoker was also higher in females (82.5%) than males (63.3%) (p=0.000). Therefore, statistical analyses were performed in order to eliminate the effects of these factors on oral ulcer activity according to both genders separately.

Female patients

The presence of oral ulcer activity was significantly lower in the severe clinical course with IS group (8.9%) compared to those of the mild course with non-IS group (63.2%), severe with non-IS group (12.7%) and the mild course with IS group whose mucocutaneous symptoms were not controlled by non-IS (15.1%) (p=0.001, p=0.003 and p=0.0011, respectively) (Table III). The number and healing time of oral ulcers were also similar in the different groups (Table IV).

In the resistant group, patients with mild disease course whose mucocutaneous symptoms were unresponsive to non-IS medications and were treated

Table II. Gender and disease-related factors according to oral ulcer activity.

		Oral ulcer inactive (n=291; 34.9%)		Oral ulcer active (n=543, 65.1%)	
		Mean	SD	Mean	SD
Disease-related factors	Age*	40.7	11.3	37.1	10.4
	Disease duration*	10.5	8.03	8.3	7.6
	Severity score*	4.9	2.2	4.2	1.7
		n	%	n	%
Gender**	Female	132	45.4	309	56.9
	Male	159	54.6	234	43.1
	Total	291	100	543	100

*p=0.000; **p=0.002

with ISs, and had the highest CI scores. In contrast, the lowest CI score was observed in the severe course with IS group (3.01±3.7) compared to other groups (p=0.005; p=0.01 and p=0.047) (Table V).

Prominent correlations were presented according to the disease pattern. The number of oral ulcers correlated with the CI score and pain status in the mild course with non-IS group (r: 0.48, p=0.000; r: 0.50, p=0.000). Healing time of oral ulcers was related to CI scores and functional status in the severe course with non-IS group (r: 0.6, p=0.000 for both) and scores of CI and pain level in severe course with IS group (r: 0.47, p=0.026; r: 0.57 p=0.005).

A significant relationship was not observed in oral ulcer activity related to smoking pattern and disease duration (p=0.12; p=0.10, respectively) (Table III). In addition, the number of oral ulcers was very similar in both groups (p>0.05). An increase in the healing time of oral ulcers was observed in non-smokers compared to smokers (p=0.02), whereas no significant relationship was observed in the other groups (p>0.05) (Table IV). Although the CI score was higher in non-smokers than current smokers, a statistically significant difference was not observed (p=0.055) (Table V).

Male patients

Oral ulcer activity was lower in the severe course with IS group (25.3%) than in the mild course with non-IS group (52.4%) (p=0.028). The severe course with IS group also had higher oral ulcer activity compared to the severe course with non-IS (7.1%) and mild course with IS group as resistant cases (15.1%) (p=0.03, p=0.048). However, the number and healing time of oral ulcers were lower in the severe course with IS (2.41±1.83; 5.88±3.49) than the severe course with non-IS group (4.28±2.78; 9.30±5.99) (p=0.011; p=0.053). Number and healing time of oral ulcers were similar in other groups (p>0.05) (Table IV). The lowest CI score was observed in the severe course with IS group (2.7±3.28) compared to the other groups (p=0.006; p=0.016 and p=0.031), but the highest CI score was present in the severe course with non-IS group (Table V).

Prominent relations were shown according to disease pattern. Healing time of oral ulcers correlated with CI scores, functional status and pain in the mild course with IS group as resistant cases (r: 0.59, p=0.000; r: 0.48, p=0.003 and r: 0.59, p=0.000, respectively). It was also related to the CI score in the severe course with non-IS group (r: 0.58, p=0.035).

Oral ulcer activity (50.2%) and poor CI score (3.99±3.26) were associated with a disease duration of less than 5 years compared to the others (p=0.002, p=0.004) (Table III and Table V). The number and healing time of oral ulcers were almost identical in the groups (p>0.05) (Table IV). In addition, no significant relationship was observed between oral ulcer activity, CI score, the number and healing time of oral ulcers related to smoking pattern (p>0.05) (Table III-V).

Female patients vs. male patients

In the mild course with non-IS group,

Table III. Oral ulcer activity related factors in patients with Behçet's syndrome.

		Female					Male				
		Oral ulcer inactive		Oral ulcer active			Oral ulcer inactive		Oral ulcer active		
		n	%	n	%	p	n	%	n	%	p
Disease course with treatment protocol	Mild + non-IS	64	52.5	184	63.2	**0.000**	63	41.7	118	52.4	**0.009**
	Mild + IS	14	11.5	44	15.1		19	12.6	34	15.1	
	Severe + non-IS	13	10.7	37	12.7		6	4	16	7.1	
	Severe + IS	31	25.4	26	8.9		63	41.7	57	25.3	
	Total	122	100	291	100		151	100	225	100	
Smoking pattern	Non-smoker	98	77.8	255	84.4	0.12	91	58.7	152	66.4	0.13
	Current smoker	28	22.2	47	15.6		64	41.3	77	33.6	
	Total	126	100	302	100		155	100	229	100	
Disease duration	< 5 years	41	32	124	59.3	0.10	54	34.6	115	50.2	**0.002**
	≥ 5 years	87	68	181	40.7		102	65.4	114	48.2	
	Total	128	100	305	100		156	100	229	100	

Table IV. Number and healing time of oral ulcers in patients according to gender.

		Female						Male					
		Number of oral ulcer			Healing time of oral ulcer			Number of oral ulcer			Healing time of oral ulcer		
		Mean	SD	*p*	Mean	SD	*p*	Mean	SD	*p*	Mean	SD	*p*
Disease course with treatment protocol	Mild + non-IS	2.96	2.83	0.50	7.27	3.62	0.90	3.22	2.80	0.06	6.51	4.02	0.22
	Mild + IS	2.75	2.08		7.82	3.75		2.88	2.29		6.63	3.32	
	Severe + non-IS	3.00	2.95		7.65	5.09		4.28	2.78		9.30	5.99	
	Severe + IS	2.62	2.61		8.38	6.51		2.41	1.83		5.88	3.49	
Smoking pattern	Non-smoker	3.06	3.06	0.29	7.82	4.25	**0.02**	2.97	2.38	0.78	6.47	3.81	0.87
	Current smoker	2.36	1.54		6.20	3.20		3.14	2.78		6.65	4.05	
Disease duration	< 5 years	3.03	3.24	0.72	7.68	3.59	0.48	2.99	2.33	0.99	6.43	3.41	0.65
	≥ 5 years	2.90	2.58		7.55	4.61		3.08	2.69		6.66	4.32	

Table V. Composite index score in patients with Behçet's syndrome according to gender.

		Female (n=441)			Male (n=393)		
		Mean	SD	*p*	Mean	SD	*p*
Disease course with treatment protocol	Mild + non-IS	4.52	3.36	**0.032**	3.73	3.24	**0.012**
	Mild + IS	4.75	3.30		4.05	3.55	
	Severe + non-IS	4.41	3.28		4.31	3.46	
	Severe + IS	3.01	3.73		2.7	3.28	
Smoking pattern	Non-smoker	4.44	3.40	0.055	3.60	3.32	0.279
	Current smoker	3.59	3.26		3.32	3.35	
Disease duration	<5 years	4.35	3.19	0.853	3.99	3.26	**0.004**
	≥ 5 years	4.27	3.57		3.09	3.36	

CI scores (Table V), functional status, pain level and healing time of oral ulcers (Table IV) were higher in females (4.52±3.36, 1.5±1.3, 2.4±1.9 and 7.27±3.62 days) compared to males (3.73±3.24, 1.2±1.3, 1.9±1.7 and 6.51±4.02 days) (p=0.021, p=0.035, p=0.008 and p=0.028, respectively). Yet, the number of oral ulcers was similar (p=0.57). This pattern was not seen in other groups (p>0.05) (Table IV).

An increase in the healing time of oral ulcers was observed in females (7.68±3.59) compared to males (6.43±3.41) with a disease duration of less than 5 years (p=0.016). A similar trend was seen in disease duration longer than 5 years (7.55±4.61 *vs*. 6.66±4.32) (p=0.04). In addition, female patients had poor CI scores (4.27±3.57) (Table V) and subscales regarding functional limitation (1.42±1.41) and pain (2.23±1.95) compared to males (3.09±3.36) (Table V); 0.93±1.27; 1.63±1.79) with disease duration more than 5 years (p=0.000, p=0.000, p=0.001). A similar trend was not seen in the early disease period (p>0.05).

In non-smokers, the healing time of oral ulcers was longer in females (7.82±4.25) than males (6.47±3.81) (p=0.001) whereas a similar trend was not seen in current smokers (p=0.74) (Table IV). Moreover, CI scores (4.44±3.40 *vs*. 3.60±3.32) (Table V), functional limitation (1.44±1.34 *vs*. 1.16±1.30) and pain (2.32±1.9 *vs*. 1.81±1.76) were found to be more impaired in females than males (p=0.004, p=0.011, p=0.000). However, no difference was observed in the number of oral ulcers in both groups in terms of gender (p>0.05).

Discussion

Since recurrent exacerbation and remission periods are a characteristic disease pattern (14, 15), the suppression of oral ulcer activity is an essential issue in the management of BS (2), This is one of the largest studies in oral ulcer assessment in BS with 834 patients from 12 different BS tertiary clinics in Turkey. Consequently, the reliability of the statistical analysis was quite high. Oral ulcer related predictive factors were first assessed according to gender. The effects of disease severity with different treatment protocols on oral ulcer activity and the Composite Index were also evaluated in four subgroups to eliminate bias with this new approach in BS. As a result, factors linked with oral ulcer activity and the Composite Index as the patient's perspective were analysed in more detail.

In the present study, a severe disease course, male gender, and an increase in age and disease duration were found to be prominent variables for inactive patients. Similarly, oral ulcer activity was observed to be negatively correlated with both immunosuppressive treatment protocols and increase in age in our previous study (2). Besides, IS treatment protocols as aggressive treatment options are commonly preferred in severe disease course, especially in male BS patients with major organ involvement and risk of mortality and/or morbidity (3).

In both genders, oral ulcer activity was associated with non-IS medication use in mild course compared to severe course with IS. Moreover, the activity was also seen in the severe course with non-IS group in the study. These relations were predicted because aggressive treatment modalities are not used in mild course with no mortality risk (16, 17). Although standard treatment protocols with low side effects are frequently used for the remission of oral ulcers, their evidence is weak. Since the primary aim of the disease management focuses on the prevention of irreversible tissue damage and life-threatening conditions in BS, patients with a severe course could be treated with non-IS medications in their remis-

sion periods (18). Among non-IS medications, complete responses for oral ulcers are unlikely in these conditions (19). In other words, oral ulcer activity may be observed in different disease courses with non-IS medication use in BS.

An increase in the number and/or healing time of oral ulcers were also associated with poor CI score in females treated with non-IS in both disease courses. Topical treatments may be helpful for these patients, however, they do not prefer them in their disease management because they only give partial relief of ulcers (19). Therefore, the impact of oral ulcers on daily life is present in this group. In contrast, the lowest oral ulcer activity and CI scores were seen in females with severe course treated with IS. Both oral activity and its effect on daily life were not prominent issues for this group because IS usage has a beneficial effect on the control of disease symptoms, especially in females.

In both genders, patients with mild course whose mucocutaneous symptoms were not controlled by non-IS were treated with IS medications for a limited period. Many systemic IS treatments such as corticosteroids, azathioprine, and biologic agents are also used for mild disease course due to resistant mucocutaneous cases with no life-threatening symptoms (20). According to the patients' perspective, a significant impact of oral ulcers was observed in this group as the highest CI scores were observed in females in the resistant group.

In our study, being a non-smoker was not a discriminative factor associated with the activity of oral ulcers in both genders. However, the ratio of non-smokers to smokers was higher in females than males. An increase in healing time of oral ulcers and CI and subgroup scores were observed to be more prominent in females than males in non-smokers, whereas the number of oral ulcers was similar in both genders among non-smokers. A similar pattern was not seen among smokers. Although smoking has beneficial effects on oral ulcer activity in BS, it leads to oral cancer (21) and severe health problems (22). The protective effect on oral ulcer occurrence in BS could be explained by the increase in the proliferation of oral epithelial cell and altered host response (23, 24). Since non-smoker females had more severe ulcer related problems, this condition is thought to be an important factor in the evaluation of treatment protocols and PROMs in clinical practice and trials.

In males, an important result was that almost a quarter of active patients had severe disease course treated with IS. Moreover, the lowest CI score and decrease in the number and healing time of oral ulcers were also found in this group. Since these patients had critical health problems regarding mortality and morbidity, a decrease in the number of oral ulcers with a rapid healing period should be a priority for these patients. Interestingly, the highest CI score was observed in the severe disease course with non-IS group. In addition, the number and healing time of oral ulcers were higher in this group compared to severe course with IS. In the present study, an unmet need for oral ulcer activity was newly identified in this group in the heterogeneity of the disease pattern. It is well known that oral microbial pathogens and their inflammatory mediators easily pass from oral ulcer sites to systemic circulation thus contributing to an inflammatory response (25, 26). Poor oral health is also found to be a significant mediator for severe disease course in males (27), therefore, a continuous activity could pose an organ risk in patients with active oral ulcers.

In males, disease duration less than 5 years was associated with both oral ulcer activity and poor CI scores. Since disease activity could not be controlled and remissions could not be achieved in the early period of the disease following the diagnosis (28), these results could be predicted. The risk of disease severity is the other critical point owing to the connection between oral ulcer environment and systemic immune response in young male patients who could potentially have new severe organ involvement (25, 26). Therefore, these results could reflect both discomfort due to oral ulcers and the risk in disease management.

Better understanding of the effects of oral ulcer activity is a critical component of disease management in BS (2). The assessment of oral ulcer activity in BS could be better performed by using PROMs which give important information about the clinical condition from the patient's perspective (29). Organ-specific PROMs are suitable in clinical practice for oral ulcers (11, 12, 30), genital ulcers (12, 30) and erythema nodosum (12) for mucocutaneous involvement. The CI as a PROM which was specifically developed for oral ulcer activity was used in this study (12). PROMs evaluate how disease symptoms and their treatment protocols affect the patient's life. They reflect the patient's perspective and/or the patient's experience regarding sign and symptoms of the underlying disease (31). Based on their location, counting oral ulcers or measuring their diameters could be a problem. In addition, it is fairly difficult to assess the effect of multiple oral ulcers with different diameters. In this perspective, the impact of oral ulcers was evaluated using the Composite Index that combines the assessment of oral ulcer-related pain and functional disability during the previous month.

In the present study, the mean score of CI was found to be 6 points, which was similar to our previous study (11). CI and its subscales were associated with oral ulcer pattern regarding the number and healing time of oral ulcers in different clinical conditions in both genders. The presence of oral ulcers as well as healing time and the number of oral ulcers could not reflect patient's condition effectively. Therefore, our results may help health professionals in the decision-making process, to understand patients' needs in clinical practice and trials and to design the best treatment protocols in clinical practice. The main limitation of the study was its multicentre nature, which may have caused patient heterogeneity from reference clinics in different cities. In addition, the data regarding oral ulcer activity was based on patient-reported measures, which may reflect subjectivity.

In conclusion, oral ulcer activity was

associated with non-IS use in both genders as well as early period of disease duration in males and resistant cases in females. Moreover, CI as an organ-specific oral ulcer activity index was associated with oral ulcer-related conditions. It helps to understand personalised needs in BS patients, as limited information is available for oral ulcers. Therefore, it might be a candidate scale to evaluate treatment efficacy for the follow-up of oral ulcer activity and future clinical studies in BS. Physicians and dentists should work together to achieve the best outcomes in disease management.

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