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The effect of colchicine on mucocutaneous and joint manifestations of Behçet's disease

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Abstract

Mucocutaneous lesions are the most common manifestation and hallmark of Behçet's Syndrome (BS). They show a significant impact on patients' quality of life and more importantly, may occur concurrently with major organ involvement. Colchicine is the first-line therapy for patients with mucocutaneous involvement because of its good tolerability and safety profile. The literature lacks clear data on the duration of treatment of mucocutaneous symptoms and the prognosis of patients who interrupt colchicine therapy. This study was planned to observe differences in mucocutaneous findings, joint findings and disease activity, in the colchicine-free period of the patients who were followed up with the diagnosis of BS without active major organ involvement and who were in remission and discontinued colchicine treatment. Our study demonstrated a significant increase in the rate of patients who developed aphthae after the discontinuation of colchicine treatment, which is the primary endpoint, and in the number of newly developed aphthae, which is the secondary endpoint. A significant increase was observed in the rate of patients who developed erythema nodosum in the first and second months. There was no significant difference in the development of genital ulcers after discontinuation of colchicine. The rate of nodular lesion development in female patients increased during the colchicine-free period. Due to the low number of patients who developed joint complaints, we could not demonstrate the efficacy of colchicine in our study.

Keywords: Behçet's syndrome, oral aphthae, colchicine

Introduction

Behçet's syndrome (BS) is a variable vascular vasculitis that can cause ulcers of the mouth and genitalia, papulopustular and erythema nodosum-like skin lesions, arthritis, uveitis, arterial aneurysms, and venous and arterial thrombosis.BS has a remitting and relapsing course [1]. The old silk route connecting the Middle East and Eastern Mediterranean to East Asia has been found to have the highest prevalence of BS. The estimated prevalence rates are recorded as 421 per 100,000 in Türkiye, 660 in Jordan, 100 in Iran, 35.0 in South Korea and 10 in China [2-6]. Despite the fact that the pathophysiology of BS is not entirely understood, it has been observed that genetic predisposition, triggering agents, and immunological abnormalities all play significant roles in its development [7]. While both men and women experience BS at almost equal rates, men are known to have a worse prognosis, more organ involvement, and higher fatality rates [8]. The disease typically manifests itself in the second or third decade of life [9]. Disease activity tends to decline over the years and approximately 60% of patients can experience complete remission within 20 years [10].

The most typical symptoms and distinguishing features of BS are mucocutaneous lesions [11]. Despite the fact that these symptoms are only mildly severe clinically, they have a considerable influence on patients' quality of life [12,13], and more crucially, they may also be associated with major organ involvement [14]. Due to the absence of an etiological agent, the treatment is carried out symptomatically. In order to avoid irreversible organ damage, the aim of treatment is to decrease inflammatory exacerbations and relapses. The severity of the disease, the involvement of the organs, the patient's characteristics, and their preferences should all be considered while choosing a course of treatment [15]. Numerous topical and systemic medications have been utilized

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for mucocutaneous and joint findings. Colchicine is the first-line treatment for patients with mucocutaneous involvement owing to its high level of safety and tolerability.

Colchicine is recommended as first-line systemic therapy, especially when erythema nodosum or genital ulcers are the most common manifestations [15]. There is no clear data in the literature on the duration of treatment of mucocutaneous symptoms and the prognosis of patients who interrupt colchicine therapy.

This study was planned to observe difference of the mucocutaneous findings, joint findings and disease activity, in the colchicine-free period of the patients who were followed up with the diagnosis of BS without active major organ involvement and who were in remission and discontinued colchicine treatment.

Material and Methods

Patients

The study included 48 patients who were diagnosed with BS based on the International Study Group Criteria [16]. The patient population consisted of patients over 18 years of age with BS who did not have active major-vital organ involvement and who discontinued colchicine treatment because of decreased and/or absent mucocutaneous manifestations associated with BS in the last 3 months compared to the past.

Methods

The study was designed as a prospective 12-week follow-up study. Patients who discontinued colchicine treatment and whose mucocutaneous manifestations were in remission were followed up once a month for three months after discontinuing the drug or were questioned by phone calls. Mucocutaneous symptoms, joint symptoms, other symptoms that may be related to BS, physical examination findings and disease activity scores were recorded in the controls performed before (0. month) and at the first, second and third months after discontinuation of colchicine. In our study, we benefited from Behcet's Disease Current Activity Form (BDCAF) and Behçet Syndrome Activity Score (BSAS) as disease activity indexes. These are validated in Turkish Behçet's patients [17,18]. The BDCAF requires clinical review; it is not a patient-based self-assessment tool. It is based on the clinical symptoms, such as fatigue, headaches, oral and genital ulcers, skin lesions, joint involvement, gastrointestinal system (GIS) involvement, eye involvement, central nervous system (CNS) involvement, major vessel involvement over the four weeks prior to assessment, as well as the patient's and doctor's overall assessment of disease activity. The overall grade is out of 12 [19]. A patient-based self-assessment tool is the BSAS. In a small percentage of BS patients, the BSAS associated with the BDCAF [20]. The 10 questions on the BSAS include visual analogue scales for the patient's level of discomfort with regard to oral ulcers, genital ulcers, and skin lesions. They also record symptoms related to the gastrointestinal, vascular, or eye involvement as well as the current disease activity and the number of oral ulcers, genital ulcers, and skin lesions present. For a total score of 0–100, the Visual Analogue Scale (VAS) questions are all rated 0–10, while the remaining questions are categorically scored (0–5, 10–response range), giving a score between 0–10. Without the doctor's input, patients complete the BSAS during their appointment with the treating physician.

The primary endpoint of our study was the rate of patients who developed oral aphthae, genital ulcer, erythema nodosum, and arthritis, whereas the secondary endpoint was an increase in the number of oral aphthae.

The descriptive statistics for the data were calculated using the following metrics: mean, standard deviation, median, minimum, maximum, frequency, and ratio values. The Kolmogorov-Smirnov test was used to determine the distribution of variables. Independent sample t-test and Mann-Whitney U test were used to analyze quantitative independent data. The Wilcoxon test was used to analyze the dependent quantitative data. The chi-square test was used to analyze qualitative independent data, and Fischer's exact test was used when the chi-square test conditions were not met. The Mc Menat test was used to analyze of dependent qualitative data. SPSS version 27.0 software was used for all analyses.

Ethical committee

The protocol was approved by the Ethical Committee of Fatih Sultan Mehmet Training and Research Hospital with protocol code FSMEAH-KAEK2022/22.

Results

The study included 48 patients, of whom 36 were female and 12 were male. The demographic and clinical characteristics of the patients are presented in Table 1.

Table 1. Demographic data of patients

		Min-Max	Mean±SD/n-%	
Age		23.0-67.0	48.7±10.5	
Age at diagnosis		19.0-52.0	35.3±9.0	
Gender	**Female**		36	75.0%
	Male		12	25.0%
Disease duration (years)		5.0-42.0	21.0±10.2	
Smoking status	**(-)**		40	83.3%
	(+)		8	16.7%
Number of patients with genital ulcers	**(-)**		11	22.9%
	(+)		37	77.1%
Number of patients with uveitis	**(-)**		34	70.8%
	(+)		14	29.2%
Number of patients with vascular event	**(-)**		44	91.7%
	(+)		4	8.3%
Number of patients with CNS involvement	**(-)**		48	100.0%
	(+)			0.0%
Number of patients with GIS involvement	**(-)**		47	97.9%
	(+)		1	2.1%

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The mean age of male patients was 48.1±11.9, and the mean age of female patients was 48.9±10.1. The mean disease duration was 20±10.9 years for males and 21.3±10.1 years for females, and the mean disease duration of the whole group was 21.0±10.2 years. There was no difference in mean age, age at diagnosis, and disease duration between genders (p>0.05).

Fourteen patients had uveitis, four patients had deep vein thrombosis (DVT) and one patient had GIS involvement, while the patients were in remission in terms of organ involvement.

Oral aphthae

The course of oral aphthae of the patients in the colchicine-free period is summarized in Table 2 and Figure 1. In the entire patient population, the mean number of aphthae and the rate of patients with aphthae in the 3-month drug-free (colchicine-free) period increased significantly compared to the last 3 months with drug use (p=0.004 and p=0.035, respectively).

Table 2. Course of oral aphthae

		Min-Max	Mean±SD	p*
Number of oral aphthae				
Last 3 months with drug use		0.0-6.0	1.4±1.7	
3-month drug-free period		0.0-10.0	2.4±2.7	**0.004**[w]
Number of oral aphthae				
Period with drug use month 0		0.0-3.0	0.5±0.9	
Drug-free period month 1		0.0-9.0	1.9±2.5	**0.001**[w]
Drug-free period month 2		0.0-15.0	1.5±2.6	**0.011**[w]
Drug-free period month 3		0.0-10.0	U±2.0	**0.039**[w]
Presence of oral aphthae			**n** **%**	
Patients with aphthae in the last 3 months with drug use	**(-)**		21 43.8%	
	(+)		27 56.3%	
Patients with aphthae in 3-month drug-free period	**(-)**		12 25.0%	**0.035**[N]
	(+)		36 75.0%	
Presence of oral aphthae				
Period with drug use month 0	**(-)**		34 70.8%	
	(+)		14 29.2%	
Drug-free period month 1	**(-)**		20 41.7%	**0.011**[N]
	(+)		28 58.3%	
Drug-free period month 2	**(-)**		22 45.8%	**0.012**[N]
	(+)		26 54.2%	
Drug-free period month 3	**(-)**		28 58.3%	**0.210**[N]
	(+)		20 41.7%	

[w]Wilcoxon test, [N]Mc Menat test, p*Comparison with the period with drug use

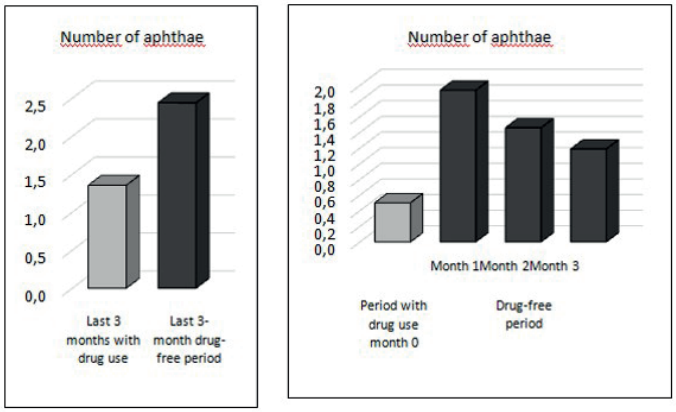

Figure 1. Numerical course of oral aphthae

The rate of patients with aphthae (p=0.011 and p=0.012), the mean number of aphthae at months 1 and 2 in the drug-free period (p=0.001 and p=0.011), and the mean number of aphthae at month 3 in the drug-free period (p=0.039) were significantly higher than those in the period with drug use.

While the rate of patients with aphthae in the last 3 months in the drug-free period increased significantly (p=0.039) compared to the last 3 months with drug use, it did not show a significant change in male patients, with no significant difference between genders. In female and male patients, the mean number of aphthae in the 3-month drug-free period increased significantly compared to that in the last 3 months with drug use (p=0.032, p=0.034, respectively). There was no discernible variation in the number of aphthae between the genders.

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The analysis of the rate of patients who developed aphthae in 1-month periods by gender showed a significant increase in the rate of patients with aphthae in the female gender group at month 2 compared to the period with colchicine use (p=0.007). There was no significant difference in the rate of patients who developed aphthae in the male gender group at months 1, 2, and 3 compared with the previous periods.

There was a significant increase in the number of aphthae in female patients at months 1, 2, and 3 after the discontinuation of colchicine treatment (p=0.004, p=0.011, and p=0.048, respectively). In male patients, an increase in the number of aphthae was observed only at month 1 (p=0.049). There was no significant difference in the number of aphthae between genders.

Twenty-one patients did not develop aphthae in the last 3 months on colchicine, and 12 of these patients developed aphthae at the 3-month follow-up without colchicine. On the other hand, 27 patients had aphthae in the last 3 months on colchicine, with a mean number of aphthae of 2.4 and with a mean number of aphthae increasing to 5 in the 3-month follow-up after discontinuation of the drug. The course of erythema nodosum, genital ulcer, and arthritis in the patients are summarized in Table 3.

Table 3. Course of joint and cutaneous manifestations

	n	%	P*
Course of arthritis			
Period with drug use	1	2.1%	
Drug-free period month l	4	8.3%	0.375[N]
Drug-free period month 2	5	10.4%	0.219[N]
Drug-free period month 3	2	4.2%	1.000[N]
Course of erythema nodosum			
Period with drug use	2	4.2%	
Drug-free period month l	9	18.8%	**0.039[N]**
Drug-free period month 2	10	20.8%	**0.008[N]**
Drug-free period month 3	3	6.3%	1.000[N]
Course of genital ulcer			
Period with drug use	0	0.0%	
Drug-free period month l	4	8.3%	0.250[N]
Drug-free period month 2	2	4.2%	0.500[N]
Drug-free period month 3	0	0.0%	1.000[N]

[N]Mc Menat test, p* Comparison with the period with drug use

Arthritis

There was no significant difference in the development of arthritis after discontinuation of colchicine from baseline in the entire population and between genders.

Genital ulcer

Similarly, there was no significant difference in the development of genital ulcers from baseline in the colchicine-free period, both in the general population and between genders.

Erythema nodosum

The number of patients who developed erythema nodosum at months 1 and 2 without colchicine showed a significant increase compared to the period with colchicine use. There was an increase in the number of patients who developed erythema nodosum at months 1 and 2 in the female patient group (p=0.031). No significant difference was observed between genders.

Disease activity

In terms of disease activity, the BDCAF index score was statistically substantially higher in female patients than in male patients at baseline (p=0.012). The BDCAF index score at months 1 and 2 in the follow-up in the general population showed a significant increase compared to the period (baseline) with colchicine treatment (p=0.046 and p=0.014, respectively). During the follow-up, there was no significant change in BSAS scores in the entire population and between genders compared to previous periods.

During the 3-month follow-up period, none of the patients showed major organ involvement. Medical treatment was arranged for patients who developed arthritis or whose quality of life was affected due to mucocutaneous manifestation during follow-up. Aphthae, genital ulcer, and erythema nodosum in one female patient, aphthae, genital ulcer, and erythema nodosum in one male patient, and aphthae, genital ulcer, and erythema nodosum in one female patient, led to the reinitiation of colchicine treatment at the end of the first month. After the treatment, patients' symptoms regressed. One male patient was initiated on prednisolone and Nonsteroidal anti-inflammatory drugs (NSAID) in the 1-month follow-up because he developed elbow arthritis, which was in remission during the follow-up. Due to an increase in the number of oral aphthae, the development of erythema nodosum and arthritis in a female patient at the 2-month follow-up, colchicine and prednisolone were initiated and the findings regressed in the follow-up.

Discussion

Our study demonstrated a significant increase in the rate of patients who developed aphthae after the discontinuation of colchicine treatment, which was the primary endpoint, and in the number of newly developed aphthae, which was the secondary endpoint. Moreover, a significant increase was observed in the number of patients who developed erythema nodosum at months 1 and 2.

Colchicine inhibits neutrophil chemotaxis, reduces TNF-α and IL-6 and exerts an anti-inflammatory effect by suppressing neutrophil function [21]. Although colchicine has been used in the treatment of joint and mucocutaneous symptoms in BS for a long time, few randomized controlled and observational studies have investigated its efficacy. Given the studies in the literature, we encounter different results.

Colchicine has been used to treat erythema nodosum and arthralgia since 1980, according to the earliest evidence of its

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effectiveness [22]. Colchicine was found to significantly reduce oral and vaginal ulcers, erythema nodosum, and joint complaints in two randomized controlled trials (RCTs) conducted in the following years [23,24].

Our research backs up the effectiveness of colchicine in treating oral aphthae linked to BS. Similarly, Davatchi et al. found regression in oral aphthae and genital ulcers in Iranian patients with BS according to the Iran Behcet's disease dynamic activity measure (IBDDAM) score, which is used as a disease activity scale [24]. In their randomized controlled double-blind study, 169 patients aged 14 years and older with a disease duration of 6 months to 23 years were included. Similar to our study design, they recorded the symptoms that disappeared during the follow-ups and reported improvement in the IBDDAM scores calculated for aphthae in the colchicine group. Another placebo-controlled randomized double-blind study by Yurdakul et al., in which 116 patients aged 18-35 years with BS, with a disease duration of 2 years or less, were observed for 24 months, only the lesions detected by the physician during the examination were recorded in terms of disease activity, and colchicine was found to be ineffective in controlling oral aphthous lesions [23]. In their placebo-controlled double-blind study, Aktulga et al. divided 28 patients into 1.5 mg/day colchicine and placebo arms, followed up for 6 months, and did not find a significant difference between the groups in terms of aphthous lesions [22].

Our study demonstrated no significant difference in the development of genital ulcers after the discontinuation of colchicine. This may be due to the small number of patients and inadequate follow-up period. Yurdakul et al., on the other hand, found colchicine effective in reducing the number of genital ulcers in female patients. Similarly, an improvement was observed in the IBDDAM score calculated for genital ulcers in Davotchi's colchicine group.

The results of our study revealed that the rate of nodular lesions development in female patients increased during the colchicine-free period. Aktulga et al. found colchicine effective in nodular lesions and Yurdakul's study found a higher number of nodular lesions in women who received a placebo. Similarly, Davotchi et al. reported a decrease in the IBDDAM score calculated for erythema nodosum in both genders in the colchicine arm.

Due to the small number of patients who have joint symptoms, we could not demonstrate the efficacy of colchicine on arthritis in our study. Aktulga et al. also found no significant difference between the groups for a similar reason. Yurdakul et al. found a higher rate of complete remission of arthritis in the colchicine arm at 24 months. Similarly, in Davotchi's study, improvement was observed in the mean IBDDAM joint score at week 16.

The small sample size and short follow-up time in our study are the main limitations. Another limitation is the small number of individuals with a range of mucocutaneous symptoms, such as genital ulcers. Comprehensive RCTs involving a larger patient populations are needed to better understand the function of colchicine in the treatment of mucocutaneous symptoms in BS.

Conclusion

In our study, we observed that BS patients whose mucocutaneous symptoms were in remission under colchicine treatment had activation of their symptoms after discontinuation of treatment. There is insufficient data in the literature on the duration of colchicine treatment in patients with persistent mucocutaneous symptoms. More comprehensive RCTs are needed to obtain adequate information on the prognosis and duration of treatment for these findings

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The protocol was approved by the Ethical Committee of Fatih Sultan Mehmet Training and Research Hospital with protocol code FSMEAH-KAEK2022/22.

References

1. Jeanette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Arthritis Rheum. 2013;65:1-11.
2. Azizlerli G, Akdağ Köse A, Sarıca R, et al.Prevalence of Behçet's disease in Istanbul, Turkey. Int J Dermatol. 2003;42:803-6.
3. Madanat WY, Alawneh KM, Smadi MM, et al. The prevalence of Behçet's disease in the north of Jordan: a hospital-based epidemiological survey. Clin Exp Rheumatol.2017;35:51-4.
4. Moghimi N, Davatchi F, Rahimi E, et al. WHO-ILAR COPCORD study (stage 1, urban study) in Sanandaj, Iran. Clin Rheumatol. 2015;34:535-43.
5. Kim JN, Kwak SG, Choe JY, Kim SK. The prevalence of Behcet's disease in Korea: data from health insurance review and assessment service from 2011 to 2015. Clin Experiment Rheumatol. 2017;35:38-42.
6. Li R, Sun J, Ren LM, et al. Epidemiology of eight common rheumatic diseases in China: a large-scale cross-sectional survey in Beijing. Rheumatology. 2012;51:721-9.
7. Pineton de Chambrun M, Wechsler B, Geri G, et al. New insights into the pathogenesis of Behçet's disease. Autoimmun Rev. 2012;11:687-98.
8. Bonitsis NG, Luong Nguyen LB, LaValley MP, et al. Gender-specific differences in Adamantiades–Behçet's disease manifestations: an analysis of the German registry and meta-analysis of data from the literature. Rheumatology. 2015;54:121-33.
9. Yazici H, Tüzün Y, Pazarli H, et al. Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behçet's syndrome. Ann Rheum Dis. 1984;43:783-9.
10. Kural-Seyahi E, Fresko I, Seyahi N, et al. The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine. 2003;82:60-76.
11. Yazici H, Seyahi E, Hatemi G, Yazıcı Y. Behçet syndrome: a contemporary view. Nat Rev Rheumatol. 2018;14:107-19. Erratum in: Nat Rev Rheumatol. 2018;14:119.
12. Fabiani C, Vitale A, Orlando I, et al. Quality of life impairment in Behçet's disease and relationship with disease activity: a prospective study. Intern Emerg Med. 2017;12:947-55.

DOI: 10.5455/medscience.2023.05.072

13. Senusi AA, Ola D, Mather J, et al. Behçet's syndrome and health-related quality of life: influence of symptoms, lifestyle and employment status. Clin Exp Rheumatol. 2017;35:43-50.

14. Seyahi E. Phenotypes in Behçet's syndrome. Intern Emerg Med. 2019;14:677-89.

15. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis. 2018;77:808-18.

16. Wechsler B, Davatchi F, Mizushima Y, et al. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet. 1990; 335:1078-80.

17. Yilmaz S, Simsek I, Cinar M, et al. Patient-driven assessment of disease activity in Behçet's syndrome: cross-cultural adaptation, reliability and validity of the Turkish version of the Behçet's Syndrome Activity Score. Clin Exp Rheumatol. 2013;31:77-83.

18. Hamuryudan V, Fresko I, Direskeneli H, et al. Evaluation of the Turkish translation of a disease activity form for Behçet's syndrome. Rheumatology. 1999;38:734-6.

19. Lawton G, Bhakta BB, Chamberlain MA, Tennant A. The Behcet's disease activity index. Rheumatology. 2004;43:73-8.

20. Forbess C, Swearingen C, Yazıcı Y. Behçet's Syndrome Activity Score (BSAS): a new disease activity assessment tool, com¬posed of patient-derived measures only, is strongly correlated with the Behçet's Disease Current Activity Form (BDCAF). Clinical and Experimental Rheumatology. 200;26:S28-S28.

21. Slobodnick A, Shah B, Pillinger MH, Krasnokutsky S. Colchicine: old and new. Am J Med. 2015;128:461-70.

22. Aktulga E, Altac M, Müftüoglu A, et al. A double blind study of colchicine in Behçet's disease. Haematologica. 1980;65:399-402.

23. Yurdakul S, Mat C, Tüzün Y, et al. A double-blind trial of colchicine in Behçet's syndrome. Arthritis Rheum. 2001;44:2686-92.

24. Davatchi F, Sadeghi Abdollahi B, Tehrani Banihashemi A, et al. Colchicine versus placebo in Behçet's disease: randomized, double-blind, controlled crossover trial. Mod Rheumatol. 2009:19:542-9.