Behçet's Disease Current Therapies: MTX- Imuran and Long-Term Effect of VIT D and Colchicine in this Population, Multi Centric Cohort Study from Aseer Region, Saudi Arabia.

Abstract

Introduction:

Behçet's disease (BD) is a rare, chronic inflammatory disorder that recurs over time, impacting multiple systems, positioning it at the intersection of autoimmune and auto-inflammatory syndromes. BD is a unique clinical entity known for its diverse manifestations with recurring oral ulcers are the most common, followed by genital ulcers.

Methods:

A comprehensive retrospective analysis was conducted on medical records and data of patients under active care in rheumatology clinics, all of whom had a confirmed diagnosis of Behçet's disease looking for their different treatment options. We defined organ involvement severity to Mild (one organ), Moderate (2 organs) and sever is 3 and more organ involvement.

Results:

111 patients, evenly distributed by gender, we analyzed therapy effects on Behçet's disease. Azathioprine and methotrexate users (54 and 13 patients, respectively) were typically aged 21-60. Colchicine use (78 patients) showed consistent results, with similar organ involvement severity. Comparatively, Vitamin D use (55 patients) showed similar age and gender distribution, with a quarter exhibiting severe organ involvement. However, neurological, gastrointestinal, and pulmonary symptoms showed no significant differences across these groups.

Conclusion:

In our study, we observed more sever disease in people taking MTX compared to Imuran. We also observed no morbidity or mortality benefit of vitamin D. Collaboration across disciplines is crucial for personalized treatment, considering organ involvement, age, gender, symptom intensity, and disease duration. The aim is precise therapies, preventing relapses, and mitigating inflammation. Larger, prospective studies are needed to compare different Conventional Disease modifying agent and to consider mortality benefits of Colchicine in BD.

Key Words:

Behcet disease, Vitamin D, Methotrexate, Azathioprine

Introduction:

Behçet's disease (BD) is a rare, chronic inflammatory disorder that recurs over time, impacting multiple systems. Its precise cause remains unknown, positioning it at the intersection of autoimmune and auto-inflammatory syndromes (1). Behçet's disease is a unique clinical entity known for its diverse manifestations. Recurring oral ulcers are the most common, followed by genital ulcers. Other clinical features include skin lesions like erythema nodosum and papulo-pustular lesions, ocular involvement (often within 2-4 years of BD onset), joint problems, gastrointestinal complications, pulmonary involvement, and cardiovascular issues such as pericarditis, myocarditis, and endocarditis. Vasculitis is a prevalent characteristic, affecting blood vessels of various sizes throughout the body. Neurological involvement, although rare, is another known manifestation of BD occurred in about 10% of them (2,3,4).

Managing Behçet's syndrome presents a challenge due to the absence of universally agreed treatment protocols, leading to potential confusion in its management. The primary treatment objective is to maintain patients in clinical remission and minimize relapses. Despite some controlled data guiding the management of arthritis, eye involvement, and mucocutaneous disease, the dearth of high-quality evidence poses a significant hurdle. Notably, there's a notable lack of evidence regarding treatment strategies for neurologic and vascular manifestations. This extends to the gastrointestinal aspect of BD, where there's a lack of internationally accepted, standardized treatment approaches (5,6,7). This article aims to explore and emphasize the diverse medication approaches for treating patients with Behçet's disease.

Methods

In this research, our primary focus was on patients who were diagnosed with Behçet's disease at Aseer Central Hospital (ACH), Military hospital and Armed force hospital in the southern region of Saudi Arabia. Utilizing a noninterventional, retrospective approach, we thoroughly examined the medical records and data of patients actively under rheumatology care, ensuring a confirmed Behçet's disease diagnosis. The inclusion criteria encompassed individuals aged 18 years and older, all diagnosed by certified rheumatologists. After a rigorous data cleaning procedure and excluding cases that did not meet the criteria, our study meticulously chose a sample of 111 patients that fulfilled the specified requirements.

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In our investigation, we carefully collected a range of patient demographic information, such as age, gender, nationality, presence of systemic involvement, were classified based

on organ involvement into three categories as mild (one organ), moderate (two organs) and sever (three and more) and symptom frequency. Our main focus was to examine the potential correlation between individuals using Azithromycin and Colchicine, along with their respective vitamin D. Ethical approval for this study was obtained from the Institutional Review Board at Aseer Central Hospital and the research committee, confirming our adherence to ethical standards in conducting this research.

Data analysis

Following the extraction of data, a rigorous process of revision, coding, and input into statistical software was meticulously carried out. Our statistical analyses adopted two-tailed tests, where a p-value below 0.05 was considered indicative of statistical significance. To investigate the association between various variables and gender, we utilized univariate analysis. Continuous variables, due to their abnormal distribution determined by the Shapiro-Wilk test, were presented as median and interquartile range. These were further analyzed using the Mann-Whitney U test. On the other hand, categorical variables were expressed as absolute numbers and proportions of cases, and their comparisons were made using either the chi-squared or Fisher's exact test. All statistical analyses were conducted utilizing the R software.

Results:

In our research, we enrolled a total of 111 patients, ensuring an equal distribution between male and female participants. To enhance comparative analysis and effectively investigate therapy-related effects and distinctions, we divided them into two groups based on three main variables: Azathioprine or methotrexate usage, colchicine usage, and vitamin D. When comparing the variables related to Azathioprine (54 patients) and Methotrexate (13 patients) usage, it was observed that a significant proportion of patients fell within the age range of 21-60 years, with an equal gender distribution in both groups. Interestingly, about two-thirds of patients in both groups exhibited elevated inflammatory markers. Notably, most individuals in the Azathioprine group had mild organ involvement, while those in the Methotrexate group presented with severe organ involvement. The majority of patients in both groups did not display skin changes, gastrointestinal symptoms, or pulmonary symptoms, as summarized in (Table 1).

In comparing patients taking colchicine (78 patients) versus those not using it (33 patients), we noted that the majority fell within the 21-60 age range, displaying an even gender distribution in both groups. Interestingly, about two-thirds of individuals in both categories showed negative inflammatory markers. Notably, the severity of organ involvement was similar in both groups, and uveitis diagnoses were comparable. Moreover, there were no significant variations in neurological, gastrointestinal, or pulmonary symptoms between the two groups (Table 2).

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Only descriptive statistical result are shown ie number and percentage of pts in each group.

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When comparing patients using Vitamin D (55 patients) versus those not taking it (56 patients), a predominant age range of 21-60 years was observed with an even gender distribution in both groups. Interestingly, about two-thirds of individuals in both categories displayed negative inflammatory markers. Notably, a quarter of the Vitamin D group exhibited severe organ involvement, while the majority showed no skin manifestations. Importantly, there were no significant differences noted between the two groups concerning neurological, gastrointestinal, or pulmonary symptoms, as well as other variables (Table 3).

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Discussion

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This study examines difference in Behçet's disease patients in regards of different long-term medications used for them, emphasizing on azathioprine, methotrexate as well as colchicine. Additionally, we explore the correlation between vitamin D usage in Behçet's disease patients on different variables. Within our study group, a notable demographic comprised individuals aged 20-40 years. This pattern is in harmony with research from Iraq (mean age 28) and various Arabic nations, such as Saudi Arabia, Jordan, and Egypt, where the age range generally centers around 25-30 years. This age trend stands in stark contrast to cohorts in non-Arabic regions, displaying higher age averages (8,9).

Treatment for Behçet's syndrome is tailored to each patient based on disease severity and organ involvement. Corticosteroids or cytotoxic drugs may be administered, supported by proven efficacy in controlled trials. While mucosal, dermal, and arthritic aspects have evidence-based treatments, ophthalmic, vascular, and neurological symptoms are managed based on clinical experience or observational studies. Azathioprine (AZA), a proven immunosuppressant, shows efficacy in treating Behçet's syndrome, particularly ocular symptoms. However, safety concerns persist, with common side effects like nausea, fever, and bone marrow suppression under debate among clinicians (10,11,12), and as consistent with previous reports, Colchicine, azathioprine, and methotrexate are commonly prescribed, either individually or in combination, for treating our Behçet's disease patients.

Colchicine is frequently used to treat mucocutaneous manifestations in Behçet's disease (BD). Clinical trials demonstrate its effectiveness in managing joint symptoms and preventing erythema nodosum, particularly in women with BD and patients without major organ involvement. However, its efficacy for mucocutaneous lesions and oral ulcers remains inconclusive, suggesting potential responsiveness in a specific subset of BD patients, as compared to other local cohort showed Colchicine is almost used for all patients (13,14,15).

Azathioprine in Behçet's Disease had a controlled trial, azathioprine was proven to be effective in reducing uveitis attacks and preserving visual acuity. Therefore, it is recommended as an initial therapy for managing posterior eye inflammation. However,

its efficacy in treating vascular manifestations needs further research, as controlled trials in this aspect are yet to be conducted (16,17). Methotrexate demonstrated efficacy in treating eye disease with a weekly dose. Additionally, it exhibited benefits for neurological involvement, although relapses were observed later on (18). Our data showed Significantly, patients in the Azathioprine group mostly had mild organ involvement, contrasting with the Methotrexate group where severe organ involvement was prevalent. The majority in both groups showed no skin, gastrointestinal, or pulmonary symptoms.

Vitamin D, an essential fat-soluble vitamin vital for immune function, plays a significant role in the pathogenesis of various inflammatory diseases, such as BD. It is intricately involved in enhancing the expression of anti-inflammatory cytokines and specific antioxidants, supported by a substantial body of evidence. Moreover, supplementation with vitamin D has shown promise in potentially improving disease severity and reducing oxidative stress in individuals with BD (19,20). In our study, intriguingly, approximately two-thirds of the patients who were taking vitamin D exhibited negative inflammatory markers. Additionally, a quarter of the patients in the vitamin D group displayed severe organ involvement, while a majority showed no skin manifestations.

Finally, commonly used medications, including Azathioprine, Methotrexate, and Colchicine, vary in effectiveness for treating ocular symptoms and mucocutaneous manifestations in Behçet's disease. Vitamin D shows potential for reducing disease severity and oxidative stress, correlating with inflammatory markers and degrees of organ involvement among patients. Multidisciplinary collaboration is vital for tailored treatment, considering organ involvement, age, gender, symptom severity, and disease duration. The objective is targeted therapies, relapse prevention, and inflammation suppression.

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Table 1: Methotrexate vs Azathioprine dependent therapy

Dependent: Methotrexate vs Azathioprine		Azathioprine	Methotrexate
		N = 54	N = 13
Age	>60	5 (9.3)	2 (15.4)
	21–40	26 (48.1)	5 (38.5)
	41–60	23 (42.6)	5 (38.5)
Gender	Female	27 (50.0)	7 (53.8)
	male	27 (50.0)	6 (46.2)
ESR	Median (IQR)	23.0 (10.0 to 34.0)	8.5 (4.5 to 31.0)
CRP	+VE	11 (32.4)	3 (30.0)
Organs involvement	Mild	23 (42.6)	2 (15.4)
	Moderate	20 (37.0)	3 (23.1)
	Severe	9 (16.7)	7 (53.8)
Muco cutaneous	Oral and genital ulcers	9 (16.7)	2 (15.4)
	Oral ulcers	19 (35.2)	8 (61.5)
	Skin pustules	0 (0.0)	0 (0.0)
Musculoskeletal	Arthritis	7 (13.0)	7 (53.8)
Eye complications	Uveitis	3 (5.6)	0 (0.0)
Neurological involvement	Headache	14 (25.9)	1 (7.7)
	Optic neuritis	0 (0.0)	1 (7.7)
	Seizure	1 (1.9)	0 (0.0)
Gastrointestinal	Abdominal pain, Rectal bleeding	1 (1.9)	0 (0.0)
	Rectal bleeding	0 (0.0)	0 (0.0)

Pulmonary	Chest pain, Shortness of breath	0 (0.0)	1 (7.7)

Table 2 Colchicine dependent therapy

Dependent: Colchicine		No	Yes
		N = 33	N = 78
Age	>60	6 (18.2)	8 (10.3)
	18–40	20 (60.6)	35 (44.9)
	41–60	7 (21.2)	35 (44.9)
Gender	Female	17 (51.5)	39 (50.0)
	male	16 (48.5)	39 (50.0)
ESR	Median (IQR)	32.0 (12.0 to 46.0)	18.0 (9.0 to 30.0)
Crp	+VE	4 (26.7)	18 (36.0)
Organs involvement	Mild	10 (30.3)	25 (32.1)
	Moderate	15 (45.5)	34 (43.6)
	Severe	7 (21.2)	16 (20.5)
Muco cutaneous	Oral and genital ulcers	4 (12.1)	19 (24.4)
	Oral ulcers	7 (21.2)	34 (43.6)
	Skin pustules	1 (3.0)	1 (1.3)
Musculoskeletal	Arthritis	5 (15.2)	16 (20.5)
Eye complications	Uveitis	5 (15.2)	6 (7.7)
Neurological involvement	Headache	9 (27.3)	19 (24.4)
	Optic neuritis	0 (0.0)	1 (1.3)
	Seizure	1 (3.0)	1 (1.3)

Gastrointestinal	Abdominal pain, Rectal bleeding	1 (3.0)	0 (0.0)
	Rectal bleeding	0 (0.0)	1 (1.3)
Pulmonary	Chest pain, Shortness of breath	9 (27.3)	8 (10.2)

Table 3 Vitamin D dependent therapy

Dependent: Vitamin D		No	Yes
		N = 56	N = 55
Age	>60	7 (12.5)	7 (12.7)
	18–40	27 (48.2)	28 (50.9)
	41–60	22 (39.3)	20 (36.4)
Gender	Female	24 (42.9)	32 (58.2)
	male	32 (57.1)	23 (41.8)
ESR	Median (IQR)	18.5 (10.8 to 37.5)	23.5 (7.0 to 33.5)
CRP	+VE	11 (39.3)	11 (29.7)
Organs_involvement	Mild	21 (37.5)	14 (25.5)
	Moderate	24 (42.9)	25 (45.5)
	Severe	10 (17.9)	13 (23.6)
Muco_cutaneous	Oral and genital ulcers	10 (17.9)	13 (23.6)
	Oral ulcers	21 (37.5)	20 (36.4)
	Skin pustules	1 (1.8)	1 (1.8)
Musculoskeletal	Arthritis	7 (12.5)	14 (25.5)
Eye_complications	Uveitis	6 (10.7)	5 (9.1)
Neurological_involvement	Headache	16 (28.6)	12 (21.8)
	Optic neuritis	0 (0.0)	1 (1.8)
	Seizure	2 (3.6)	0 (0.0)
Gastrointestinal	Abdominal pain, Rectal bleeding	0 (0.0)	1 (1.8)

	Rectal bleeding	0 (0.0)	1 (1.8)
Pulmonary	Chest pain, Shortness of breath	10 (12.5)	10 (18.2)

Dependent: Vitamin_D		No	Yes	p
		N = 56	N = 55	
Organs_involvement	Mild	21 (37.5)	14 (25.5)	0.439
	Moderate	24 (42.9)	25 (45.5)	
	Severe	10 (17.9)	13 (23.6)	

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