



Evaluation of treatment adherence in patients with Behçet's disease: its relation to disease manifestations, patients' beliefs about medications, and quality of life

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Abstract

Introduction/objectives Despite its importance, adherence to treatment has not been sufficiently studied in Behçet's disease (BD). The aim of this study was to evaluate medication adherence in BD using the Compliance Questionnaire of Rheumatology (CQR) and factors potentially affecting it.

Method This cross-sectional study included 67 consecutive BD patients including 57 (85%) males with a mean age of 35.1 ± 9.27 years and mean disease duration of 129 ± 91 months. The cumulative clinical manifestations, the Behçet's Disease Current Activity Form (BDCAF) score, and the Vasculitis Damage Index (VDI) were recorded. The CQR, Socioeconomic Status Questionnaire for Health Research in Egypt (SES), the Beliefs about Medication Questionnaire (BMQ), and the Short Form 36 (SF-36) quality of life assessment questionnaire were administered to the patients. Linear regression analysis was done to determine independent predictors of CQR.

Results The mean BDCAF score was 3.27 ± 3.54 and the VDI was 3.36 ± 2.21 . The mean CQR score was 69.2 ± 11.79 . The CQR score varied significantly among different health sources ($p = 0.02$), with no relationship detected with other sociodemographic characteristics, nor with clinical characteristics or the SF-36. Among the investigated medications' complexities, severity of side effects showed significantly different CQR scores ($p = 0.004$), and a weak positive correlation between medications' numbers and the CQR was detected. Predictors for higher CQR scores included the necessity beliefs score of the BMQ ($\beta = 1.1, p < 0.001$); whereas, predictors for lower CQR scores were the harm and concern BMQ subscales ($\beta = -1.5, p = 0.004$) and ($\beta = -0.72, p = 0.032$), respectively).

Conclusions Beliefs about medications were the only predictor for adherence in our cohort.

Keywords Adherence · Behçet's disease · Beliefs about medications · Compliance · Quality of life

Introduction

Behçet's disease (BD) is a chronic autoimmune systemic vasculitis with an obscure pathogenesis, which is characterized by multisystem involvement that could lead to serious morbidity and mortality [1, 2]. Hence, administration of optimum management in a timely manner is crucial to hamper irreversible tissue damage. Medication adherence is vital to achieve these therapeutic goals, and thus improve disease outcomes

[3]. It could be defined as the extent to which patients abide by the day-to-day treatment, with respect to the prescribed schedule, dosage, and frequency [4].

Adherence is quite intricate, being influenced not only by the nature and/or mode of administration of the implemented medications nor by the disease pattern, severity, and/or duration, but also could be influenced by numerous interrelated factors such as sociodemographic, clinical, and psychological characteristics of patients, and their beliefs about medications [5, 6].

Adherence is particularly challenging in chronic diseases, including rheumatic diseases [7], owing to their complex nature, which usually necessitates prolonged periods of poly-medication, and are often characterized by the co-occurrence of multi-morbidity [8].

Low rates of adherence have been reported in various rheumatic diseases, ranging from 20 to 90% [9–15]; thus, leading

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to several consequences ranging from a direct impact on patients' quality of life [14–18], to the augmentation of healthcare national challenges such as cost and resources [16–18].

Despite its importance, adherence to treatment and the factors affecting it have been addressed rather scarcely in BD [7, 19–21]. The purpose of this study was to investigate medication adherence in patients with BD using the Compliance Questionnaire of Rheumatology (CQR) [22], which is to our knowledge, the only adherence measure specifically developed for use in rheumatic diseases [23], and aiming to identify possible predictors of nonadherence.

Patients and methods

Sixty-seven consecutive patients with Behçet's disease were included in this study. They were interviewed during their visit to the Rheumatology and Rehabilitation outpatient clinic or during their admission in the inpatient department at Kasr Al Ainy Hospital, Cairo University, from July to December 2017. Patients were diagnosed according to the International criteria of Behçet's Disease (ICBD) of 2014 [24]. Patients with life-threatening conditions, severe mental affection, less than 16 years old, and/or having a disease duration less than 3 months were excluded. The purpose of this study was explained to all participants. Confidentiality was assured, and verbal informed consent was obtained. The study was approved by the local Ethics Committee, according to the provisions of the World Medical Association Declaration of Helsinki.

Sociodemographic data were obtained from the patients: age at the time of conducting the study; age at disease onset which was defined as the age at the time of development of manifestations; disease duration: was calculated from the disease onset till the last recorded visit; and marital status. Information related to residence, educational level, occupation, and health care source were obtained according to socioeconomic status (SES) questionnaire for health research in Egypt [25].

The cumulative clinical manifestations were recorded. Disease activity was assessed through the Behçet's Disease Current Activity Form (BDCAF) [26], which measures clinical manifestations according to the duration of each symptom in the 4 weeks prior to assessment, with ocular and vascular activity and major vessels involvement being assessed as dichotomous variables. Organ damage at the time of the study was assessed through the Vasculitis Damage Index (VDI) [27], which is based on the accumulation of non-healing scars due to the disease, disease treatment, or comorbidity irrespective of the cause. These manifestations were recorded if they occurred after the diagnosis of vasculitis was made and lasted for at least 3 months, or were recorded if they occurred at least

3 months prior to the assessment in the case of episodic events. Treatment received by the patients at the last visit was recorded. Side effects to treatment, if reported, were classified into mild (transient or mild discomfort with no limitation in activity), moderate (daily activity is affected mildly to moderately with no or minimal medical intervention needed, or severe (daily activity is markedly reduced and medical intervention or hospitalization is needed) [28].

The quality of life (QoL) of the patients was evaluated using the Short Form-36 (SF-36) [29] electronic form of the Arabic version of SF-36 provided by the Research and development Health Corporation was used to calculate the SF-36 scores. (https://www.rand.org/health/surveys_tools/mos/36-item-short-form.html).

Patients' beliefs about medications were assessed using the Beliefs about Medication Questionnaire (BMQ) [30], which has been validated in Arabic [31]. It consists of a specific part (related to medications prescribed for the current disease) and a general part (related to the attitude of the patients towards medicines in general). The specific part includes the specific-*necessity* and specific-*concern* subscales, while the general part comprises the general-*harm* and the general-*overuse* subscales.

Adherence to treatment was assessed through the Compliance Questionnaire of Rheumatology (CQR) [22], which consists of 19 items that have been translated into Arabic, with a modification applied to item 16 in order to fit our target population. which was modified as follows: "I organize my medication doses some way" because dose organizers are not commonly used in Egypt. The CQR is a continuous scale ranging from 0 (complete noncompliance) to 100 (perfect compliance).

Statistical analysis

Data were coded and entered using the statistical package SPSS version 25. Data were summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired *t* test when comparing two groups and analysis of variance (ANOVA) with multiple comparisons post hoc test when comparing more than two groups. Correlations between quantitative variables were done using Pearson correlation coefficient. Linear regression analysis was done to predict independent predictors of CQR. *p* values less than 0.05 were considered as statistically significant.

Results

This cross-sectional study included 67 patients diagnosed as BD, of whom 57 (85%) were males and 10 (15%) were

females. Mean patients' age was 35.1 ± 9.27 (range 20–70) years, while the mean age at onset was 23.7 ± 6.54 (range 11–40) years. The mean disease duration was 129 ± 91 (6–480) months. The detailed sociodemographic features of the patients are shown in Table 1.

The prevalence of the cumulative clinical manifestations is shown in Table 2. Comorbidities were present in 15 (22.4%) patients, of whom 8 (53%) were hypertensive, 6 (9%) had diabetes mellitus, while 5 (7%) patients had other comorbidities which were viral hepatitis B and (1 patient (1.5%)) C viral infections (1 patient (1.5%)), thyroid dysfunction (1 patient (1.5%)), and tuberculosis (2 patients (3%)).

The general disease activity score of the patients was assessed by the BDCAF which ranged from 0 to 22 with a mean of 3.27 ± 3.54 . Active ocular involvement was found in 12 (18%) patients, and active vascular disease in 4 (6%); whereas, none of the patients had active neurological disease in the 4 weeks prior to assessment.

The VDI ranged from 0 to 9 with a mean of 3.36 ± 2.21 . The most frequent damage was visual impairment being present in 41 (61%) of the patients, which reached to loss of vision in one eye in 17 (25%), and complete loss of vision in 6 (9%) patients. Cerebrovascular accidents were the second most common damage being present in 11 (16%) patients, including 7 (10%) patients with dural sinus thrombosis.

Medications

The most commonly used medications for treatment of BD in our cohort were glucocorticoids (GC) that were received by almost all patients 66 (99%). Patients received a mean number of 4.63 ± 1.73 (1–9). Names of medications are shown in Table 2. Side effects were present in 34 (50.7%) patients, of whom 29/67 (43.3%) and 5/67 (7.5%) had mild and moderate side effects, respectively. None of the patients had severe or life-threatening side effects. The most prevalent side effects were GC-related side effects (34 (50.7%)) in the form of gastritis (25 patients (37%)), GC-induced diabetes (4 patients (6%)), and hypertension (6 patients (9%)), cataract (3 patients (4%)), truncal obesity (1 patients (1.5%)), and osteoporosis (1 patient (1.5%)); other drug related side effects were infections due to immunosuppression (11 (16.4%)), and warfarin toxicity (1 (1.5%)).

Quality of life

Of the eight health concepts assessed by SF-36 QoL questionnaire, physical functioning showed the highest mean (82.98 ± 14.95). The means for the SF-36 QoL subscales are shown in Table 3.

Table 1 Sociodemographic characteristics of the patients

Sociodemographic characteristics	N = 67 (%)
Gender	
Females	10 (15)
Males	57 (85)
Marital status	
Married	52 (77.6)
Single/divorced/separated	15 (22.4)
Education level	
Illiterate	5 (7.5)
Read and write	5 (7.5)
Primary school	14 (20.9)
Preparatory	4 (6)
Secondary school	35 (52.2)
High school	3 (4.5)
University degree	1 (1.45)
Occupation	
Unemployed	25 (37.3)
Unskilled manual worker	20 (29.9)
Skilled manual worker/farmer	9 (13.4)
Trades/business	6 (9)
Semiprofessional/clerk	7 (10.4)
Health care	
Traditional/self-care	16 (23.9)
Free governmental service/health insurance	33 (49.2)
More than one health care source	18 (26.9)
Residence	
Urban slum	9 (13.4)
Rural	21 (31.3)
Urban	37 (55.5)

Beliefs about medication

The *necessity* score of the specific component of the BMQ showed the highest mean (19.5 ± 4.3); whereas, the lowest mean belonged to the *harm* score of the general component of the BMQ (7.3 ± 2.32). Components and subscales of the BMQ are shown in Table 3.

Compliance questionnaire of rheumatology

The CQR score ranged from 33.33 to 87.72, with 15/67 (22%) of the patients scoring > 80. The mean of the score was 69.2 ± 11.8 ; whereas, the median (the 50th percentile value) was 70 (interquartile ratio (IQR) 63.16–78.94).

Association of variables with the CQR score

Of the investigated sociodemographic features, age ($r = -0.009$, $p = 0.94$), age at onset ($r = -0.19$, $p = 0.1$), and disease

Table 2 Cumulative clinical characteristics and medications' types and route of intake

Clinical characteristics	<i>N</i> = 67 (%)
Clinical manifestations	
Oral ulcers	67 (100)
Genital ulcers	64 (95.5)
Other skin	46 (68.7)
Ocular	47 (70)
Vascular	26 (39)
Cardiopulmonary	10 (15)
Neurological	15 (22.5)
Gastrointestinal	6 (9)
Articular	41 (61)
Comorbidities	15 (22.4)
Medications	
Types	
Glucocorticoids	66 (98.5)
Colchicine	24 (35.8)
Azathioprine	28 (41.8)
Methotrexate	7 (10.4)
Cyclophosphamide	5 (7.5)
Infliximab	11 (16.4)
Cyclosporine	13 (19.4)
Anticoagulation	16 (23.9)
NSAIDs (including low-dose aspirin)	18 (26.9)
Parenteral intake	16 (23.9)

NSAIDs non-steroidal anti-inflammatory drugs

Table 3 Components of the Short Form-36 (SF-36) Quality of Life (QoL) subscales and the Beliefs About Medications Questionnaire (BMQ)

SF-36 QoL subscales	Mean ± SD
1. Physical functioning	82.98 ± 14.95
2. Role of limitation due to physical health	38.99 ± 36.44
3. Emotional wellbeing/mental health	54.626 ± 19.26
4. Role of limitation due to emotional problems	50.75 ± 39.50
5. Social functioning	65.74 ± 28.67
6. Energy/vitality	48.58 ± 17.03
7. Bodily pain	57.014 ± 25.25
8. General health	54.55 ± 16.59
• Physical component summary (PCS)	65.54 ± 15.81
• Mental component summary (MCS)	53.53 ± 19.81
BMQ subscale	Mean ± SD
I. Specific beliefs	
• Necessity score	19.43 ± 4.38
• Concerns score	14.58 ± 3.58
II. General beliefs	
• Overuse score	11.39 ± 3.48
• Harm score	7.3 ± 2.32

duration ($r = 0.1$, $p = 0.42$) did not show any correlation with the CQR; moreover, gender differences, variation in educational and occupational levels, and residence showed no relationship with the CQR score (Table 4). On the other hand, the source of health care was the only factor showing an association with the CQR ($p = 0.02$) in which self-funded patients showed the lowest CQR score. None of the investigated clinical characteristics showed an association with the CQR (Table 5), and there was no significant correlation between the CQR and the BDCAF ($r = -0.73$, $p = 0.55$) or the VDI ($r = -0.87$, $p = 0.482$). Although no medication in particular showed an association with the CQR nor did parenteral route of intake (Table 5), medication's number showed a positive, yet weak correlation with the CQR ($r = 0.24$, p value = 0.046). CQR scores significantly varied according to the severity of medications' side effects ($p = 0.004$) (Table 5).

None of the eight health concepts of the SF-36 showed correlation with the CQR (Table 6). On the contrary, all BMQ subscales, excluding the general-overuse score, showed a strong significant correlation with the CQR (Table 6), with the specific-necessity BMQ subscale showing a strong positive correlation ($r = 0.477$, $p < 0.001$), and the specific-concern and the general-harm BMQ domains showing a negative one ($r = -0.32$, $p = 0.008$) ($r = -0.42$, $p < 0.001$), respectively). Moreover, upon using linear regression analysis, they were the only predictors for higher or lower CQR scores, with the necessity subscale of the specific BMQ score being a predictor for higher adherence ($\beta = 1.1$, $p < 0.001$), and the specific-concern and general-harm subscales predictors of lower CQR scores ($\beta = -0.72$, $p = 0.03$) and ($\beta = -1.5$, $p = 0.004$), respectively).

Discussion

Behçet's disease is a complex autoimmune disease in which successful management relies on several factors, including adherence to treatment [19], which if unmet, could lead to grievous outcomes.

A wide variety of direct [32] and indirect methods [33] have been used to assess adherence; however, there is no consensus on which tool to implement [34]. In our study, treatment adherence was assessed using the CQR [22]. Although it is the only specific validated adherence questionnaire for rheumatic diseases [35], it was not originally designed to classify patients into adherent and non-adherent. Hence, dichotomizing its continuous scale (from 0 to 100) in order to divide patients according to their adherence showed inconsistency among various studies encompassing different rheumatic diseases, with some authors determining adherence rates at 80% [36–38] or 60% [10] of the CQR scale, while others setting the 50th percentile of the score achieved as the cutoff level [39, 40].

Table 4 Association of the Compliance Questionnaire of Rheumatology (CQR) scores with the studied sociodemographic characteristics of the patients

Sociodemographic characteristics	CQR score (mean (SD))	<i>p</i> value*
Gender		
Male	68.5 (12.2)	0.27
female	72.9 (8.52)	
Marital status		
Single	67.95(11.85)	0.939
Married/divorced/separated	69.57(11.87)	
Education		
Illiterate	73.6 (6.6)	0.52
Read and write	67 (11.1)	
Primary	64.4 (15)	
Preparatory	68.8 (4.3)	
Secondary	69.9 (11.7)	
High school	78.3 (4)	
University	73.6	
Occupation		
Unemployed	71.7 (8)	0.07
Unskilled manual worker	66.7 (14.9)	
Skilled manual worker/farmer	69.2 (9.4)	
Trade/business	59.3 (13.52)	
Semiprofessional/clerk	75.6 (10)	
Health care source		
Traditional/self-care	62.7 (15.8)	0.028*
Free governmental service/health insurance	70.28 (10.5)	
More than one source	73 (7.42)	
Residence		
Rural	70.34 (11)	0.57
Urban slum	71.9 (7.7)	
Urban	67.9 (13)	

*Significant *p* value < 0.05

In our study, the mean score of the CQR was 69.2 ± 11.79 . Cinar et al. [20] found a comparable mean CQR (66.48 ± 13.49) among their Turkish BD patients, and further assessment of adherence using the Morisky Medication Adherence Scale-8 (MMAS-8) revealed that about 80% of their patients had medium/high and 20% low adherence scores. Another study from Turkey using the MMAS-8, however, showed medium/high adherence levels in 17.3% and low adherence in 82.7% of their patients, respectively [21]. On the other hand, upon applying a self-reported questionnaire and an appointment keeping behavior, Khabbazi et al. detected adherence rates of about 50% [7].

In our study, health care sources were the only sociodemographic factor showing significantly different CQR scores, with the lowest score belonging to self-funded patients. These findings are in agreement with a former study, which reported that the cost of medications was the cause of nonadherence in 14.6% of the patients [7]. Age, age at onset, gender, residence, educational level, and occupation, however, showed no relationship with the CQR score, which is in

line with a previous report [20], whereas contradictory to another that showed a significantly lower income and a male predominance among non-adherent patients [7]. There was variation in the relationship of the disease duration with adherence among various rheumatic diseases [5, 9–11, 15], with a previous study showing an association with adherence [15], and several others showing no relationship [9–11]. There was no difference between adherent and non-adherent BD patients in various studies [7, 20, 21], which is similar to our cohort.

Clinical characteristics, including disease activity and damage scores, were not related to adherence which is in agreement with Khabbazi et al. [7]. Other investigators, however, found treatment adherence to be higher among BD patients with ocular involvement when compared to those with isolated mucocutaneous involvement [21].

The importance of treatment adherence stems from its potential impact on the QoL [38, 41], a relationship that to the best of our knowledge has not yet been investigated in BD; however, no correlation was found between any of the components of the SF-36 and the CQR scores.

Table 5 Differences in the mean Compliance Questionnaire of Rheumatology (CQR) scores among the investigated clinical characteristics and medications' types and route of intake

	CQR		<i>p</i> value*
	Presence Mean (SD)	Absence Mean (SD)	
Clinical characteristics			
Clinical manifestations			
Oral ulcers	69.2 (11.8)	–	–
Genital ulcers	68.9 (11.9)	75.4 (4.6)	0.35
Other skin manifestations	69.9 (9.7)	67.5 (15.4)	0.5
Ocular	68.2 (12.6)	71.5 (9.3)	0.286
Vascular	70.5 (9.3)	68.38 (13.1)	0.47
Cardiopulmonary	71.23 (9.2)	68.8 (12.2)	0.56
Neurological	68.54 (12)	69.4 (11.85)	0.8
Gastrointestinal	75.1 (7.1)	68.62 (12)	0.198
Articular	69.7 (11.3)	68.2 (12.5)	0.615
Comorbidities	70.9 (12)	68.6 (11.8)	0.5
Medications			
Glucocorticoids	68.98 (11.7)	84.2	0.2
Colchicine	71.2 (9.6)	68 (12.8)	0.3
Azathioprine	70 (10.2)	68.6 (12.9)	0.62
Methotrexate	66.6 (4.1)	69.5 (12.3)	0.22
Cyclophosphamide	70.1 (6.4)	69.1 (12.1)	0.85
Infliximab	70.6 (8.9)	68.9 (12.3)	0.66
Cyclosporine	71.1 (11.5)	68.7 (11.9)	0.51
Anticoagulation	70.9 (9.1)	68.6 (12.5)	0.5
NSAIDs	67.9 (9.3)	69.6 (12.6)	0.59
Parenteral intake	70.5 (8)	68.8 (12.7)	0.61
Side effects			
Absent**	70.9 (9.3)	47.3–84.2	0.004*
Mild***	70 (11)	40.3–87.7	
Moderate***·***	52.9 (19.7)	33.3–82.46	

NSAIDs non-steroidal anti-inflammatory drugs

*Significant *p* value <0.05; ***p* = 0.004; ****p* = 0.006

One of the major barriers of adherence to treatment is the complexity of the treatment regimen itself, particularly in chronic diseases, in which medications are frequently associated with poly-pharmacy, frequent dosing, and/or presence of side effects [7, 42].

In the present study, the type of the medications used showed no association with the CQR score, while a previous report demonstrated that non-adherent patients showed a higher frequency of NSAIDs intake [7]. Parenteral route of intake showed no relationship with adherence, a factor that to our knowledge has not been studied among BD patients; however, the route of drug administration has been shown to affect adherence among various chronic and rheumatic diseases [5]. Unexpectedly, the number of medications showed

Table 6 Correlation of the SF-36 and beliefs about medications with the mean CQR score

	<i>r</i>	<i>p</i> value*
SF-36		
1. Physical functioning	0.51	0.68
2. Limitation due to physical health	–0.112	0.36
3. Limitation due to emotional problems	0.79	0.5
4. Energy/vitality	0.39	0.75
5. Emotional wellbeing	0.1	0.388
6. Social functioning	0.22	0.07
7. Pain	–0.53	0.69
8. General health	0.17	0.15
•Physical component summary	0.075	0.54
•Mental component summary	0.126	0.31
BMQ		
I. Specific score		
Necessity score	0.47	<0.001*
Concern score	–0.32	0.008*
II. General		
Overuse score	0.14	0.25
Harm Score	–0.42	<0.001*

SF-36 Short form-36, BMQ beliefs about medications

*Significant *p* value <0.05

a weak positive correlation with the CQR score, which is contradictory to a previous report showing a higher frequency of medication's numbers among non-adherent patients [21].

It is of note that CQR scores among patients with absent, mild, or moderate side effects showed statistically significant differences, with patients with no side effects showing the highest CQR score, which is in line with another study that reported the presence of medications' side effects to be the leading cause of nonadherence (24.1%) among BD patients [7].

Adherence to treatment could be viewed as a balance between the beliefs of patients about the necessity of medications and the fear of their side effects [43]. Indeed, beliefs about the *necessity* of medications, a subscale of the BMQ-specific part, showed a positive correlation with the CQR score ($r = 0.47$, $p < 0.001$); whereas, the fear of developing side effects (assessed through the *concerns* score of the specific component of the BMQ) and the beliefs about medications' *harm* (of the BMQ-general scale) showed a significant negative correlation ($r = -0.32$, $p = 0.008$) ($r = -0.42$, $p < 0.001$), respectively). Moreover, on linear regression analysis, the specific necessity and the concern and harm scores were the only predictors of CQR scores.

In this respect, Cinar et al. [19] reported that specific necessity scores were significantly higher in patients with high/medium adherence compared to those with low adherence. Moreover, the authors detected significant differences

between high/medium adherence and low adherence patients in the specific-concern and general-overuse subscales of the BMQ. In line with these findings, Khabbazi et al. reported that the mere fear of developing side effects accounted for nonadherence in 8% of their patients [7].

The main limitation of this study lies in the limited number of patients. On the other hand, the strengths of the study include the use of the CQR, a specific adherence measure designed for patients with rheumatological conditions, studying socioeconomic and clinical aspects of the disease, and including the patient perspective through assessing quality of life and the patients' beliefs about medications.

To conclude, among the studied factors, beliefs about medications' necessity and harm and the concern about their side effects are predictors of adherence in BD.

Compliance with ethical standards

The study was approved by the local Ethics Committee, according to the provisions of the World Medical Association Declaration of Helsinki.

Disclosures None.

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