Non-adherence to colchicine treatment is a common misevaluation in familial Mediterranean fever

Abstract

Background: Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease that requires lifelong colchicine treatment. Colchicine is the mainstay of the treatment which decreases the frequency and the severity of recurrent FMF attacks, also, prevents the development of amyloidosis. This study aimed to investigate the rates of colchicine treatment adherence in patients with FMF and the factors related to treatment non-adherence.

Materials and methods: This observational study was conducted with 179 patients with FMF between November 2018 and April 2019 in a tertiary rheumatology outpatient clinic. The sociodemographic and clinical data were recorded. Compliance Questionnaire on Rheumatology (CQR) was used to assess the treatment adherence and the Beliefs About Medicines Questionnaire (BMQ-T) was used to assess a patient's beliefs about colchicine. The factors associated with adherence to the treatment were evaluated.

Results: The study included 113 male (63.1%) and 66 (36.9%) female patients with a mean age of 30 (25-44) years. The rate of the patients who declared regular colchicine usage was 66.5%. The frequency of non-adherent patients was 83.8% according to CQR. Treatment adherence was better in patients with comorbid diseases than those without (41.4% vs. 22%, respectively, $p = 0.028$). The frequency of married patients in the adherent group (72.4%) was higher than the non-adherent group (47.3%) ($p = 0.013$). The colchicine dose used in the adherent group was 1.5 (1.3-1.8) mg/day, whereas it was 1.5 (1.0-1.5) mg/day in the non-adherent group ($p = 0.033$). The

adherence rate was rising with increasing scores of BMQ-T Specific Necessity. As the scores of BMQ-T General Overuse and General Harm increased, non-adherence to colchicine increased.

Conclusion: Evaluating adherence to colchicine treatment with objective methods is crucial to ensure sufficient treatment and prevent amyloidosis. Determining beliefs about colchicine may increase patients' adherence to treatment.

Keywords: Adherence, familial Mediterranean fever, colchicine

1. Introduction

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease with recurrent febrile attacks with peritonitis, pericarditis, pleuritis, arthritis, and erysipelas-like erythema. The disease is frequent among Turks, Armenians, Arabs, and Jaws;with a reported prevalance of 0.093% in Turkey [1,2]. Colchicine is the mainstay of FMF treatment due to being easy to use, safe and cheap, and plays a crucial role in both decreasing the frequency and severity of febrile attacks also preventing the development of amylodiosis [3]. The frequent attacks and ongoing subclinical inflammation lead to the development of amyloidosis, most significant complication of FMF, may be responsible for chronic kidney disease and increased rate of mortality among patients. However, approximately 5% of FMF patients are unresponsive to colchicine treatment and they require biological drugs [4]. It is important to determine the real colchicine resistance. The main reason for unresponsiveness to colchicine treatment is using colchicine non regularly [5]. Colchicine non-adherence may cause unsatisfactory management and worsened outcomes, such as the development of complications, decreased quality of life, or increased costs for treatment [3,6,7]. Since the biological agents are much more expensive and have own risks, non-adherence to colchicine is a non-negligible factor for classifying a patient as unresponsive. Therefore, the factors related to non-adherence to colchicine are problems that have to be overcame primarily. Non-adherence to treatment may be intentional due to the motivation, chocies and beliefs of the patient, or, may be unintentional due to the insufficient knowledge, inability and low capacity of the patient. Beliefs About Medicines Questionnaire (BMQ) was developed to determine the patients who were non-adherent to the treatment due to intentional factors [8]. In this context, intentional non-adherence to colchicine is associated with causes depending on patients' beliefs about medications and illness. So

that, patients' beliefs about colchicine may be crucial in achieving treatment adherence and treatment success. The current study aimed to determine the rates of colchicine treatment adherence and related factors in patients with FMF.

2. Materials and Methods

2.1. Design of the study, patient selection and data collection

This cross-sectional observational study enrolled 179 patients with FMF who were following up at the rheumatology outpatient clinic of Gülhane Training and Research Hospital between November 2018 and April 2019. The patients who were diagnosed with FMF according to Tel-Hashomer criteria [9], aged ≥ 18 years old, who could speak, write in and read in Turkish were included in the current study. Verbal and written informed consent forms were obtained from each patient before including the study in accordance with the principles of the Helsinki Declaration. Exclusion criteria were; having a psychiatric disease, malignancy, cognitive dysfunction, and being pregnant. The study was approved by the Local Ethical Committee of Gülhane Training and Research Hospital (approval number is 18/281). The sociodemographic and clinical data were obtained from patients' files and also, through face-to-face interviews. Compliance Questionnaire on Rheumatology (CQR) and the Turkish version of Beliefs About Medicines Questionnaire (BMQ-T) forms were applied to patients by the same interviewer and took approximately 15-20 minutes. The patients who had one and more FMF attacks each month despite receiving colchicine in maximum tolerated doses during six months are defined as colchicine resistant [10].

2.2. Compliance Questionnaire on Rheumatology

CQR has developed by Klerk et al. to assess the treatment adherence of patients with rheumatologic disease [11]. It was translated to Turkish and validated by Cinar et al

[12]. CQR consists of 19 items according to the treatment adherence of the patients. The interviewer asks the patient to state the degree of their agreement with each statement on a 4-point Likert-type scale. Each statement is pointed from 1-4 point; ranging from strongly disagree [1] to strongly agree [4], but the items numbered 4, 8, 9, 11, 12, and 19 are negatively stated and should be recoded reversely (4 = 1, 3 = 2, 2 = 3, 1 = 4) to provide a positive score. A score ranging from 0 to 100 is calculated by subtracting 19 from the sum of the items and dividing by 0.57. Higher scores predict higher rates of compliance with the treatment for patients with rheumatologic diseases. A score of 0 indicates no compliance, on the other hand, a score of 100 indicates perfect compliance. Non-compliance is defined as a score equal to or less than 80 [11].

2.3. Beliefs About Medicines Questionnaire

Beliefs About Medicines Questionnaire (BMQ) evaluates the patients' expectations and perceptions about medications in two sections, BMQ Specific and BMQ General. BMQ was validated by Cinar et al. for the Turkish population (BMQ-T). The BMQ-T has a total of 18 items. BMQ-T Specific and BMQ-T General sections have two subgroups for each. BMQ-T Specific consists of Specific-Necessity and Specific-Concern which assess the beliefs and concerns about a patient's personal disease and medications. BMQ-T General consists of General-Harm and General-Overuse, and assess the patient's general beliefs and perceptions about medications. A 5-point Likert scale is used to assess the agreement for each statement ranging from strongly disagree [1] to strongly agree [5]. There were 5 statements for each in BMQ-T Specisific-Necessity and Specific-Concern, and 4 statements for each in BMQ-T General-Harm and General-Overuse. For each subgroup, an average score is calculated. Higher scores indicate stronger belief for the calculated section [6,8].

2.4. Statistical Analysis

IBM SPSS statistic 21 was used for statistical analysis. The compatibility of the continuous data with a normal distribution was examined using the Kolmogorov-Smirnov test. Descriptive statistics were presented as mean±standard deviation or median (25^{th} and 75^{th} percentiles) values for measured variables, and frequency and percentage (%) for categorical data. The Spearman correlation coefficient was used to evaluate the association between variables. Mann-Whitney U test, Pearson Chi-Square test, and Fisher's Exact test were used for analyzing the data. A p value less than 0.05 was accepted as statistically significant.

3. Results

A total of 179 (113 Male/ 66 Female) patients were included in the study. The median age was 30.0 (25.0-44.0) years, and the median disease duration was 15.0 (9.0-22.0) years. The median time for diagnosis delay was 3.0 (1.0-9.0) years. Clinical manifestations were peritonitis in 156 (87.2%) patients, fever in 154 (86%) patients and artralgia in 104 (58.1%) patients. Other clinical manifestations were presented in Table 1. One hundred fifty-five (91.7%) patients had a mutation in the Mediterranean fever (MEFV) gene. The most common mutation was M694V in 119 (66.5%) patients. Proteinuria was detected in 25 (14%) patients. Eight (4.5%) patients had amyloidosis (Table 1).

The median dose of colchicine was 1.5 (1.0-1.5) mg/day. The percentage of the patients who declared that they have been using colchicine regularly was 66.5%. Colchicine resistance was present in 21 (11.7%) patients. Forty (22.3%) patients reported an adverse event due to colchicine. The most frequent adverse event was diarrhea in 23 (12.8%) patients. The other adverse events were abdominal pain (2.8%), vomiting (1.1%), hair loss (1.1%), vitamin B12 deficiency (1.1%), myopathy (1.1%), elevation of

liver transaminases (0.6%), constipation (0.6%), arthralgia (0.6%) and urticaria (0.6%) (Table 1).

The mean score of CQR was 67.4 ± 11.7 in the study group. According to CQR, the number of non-adherent patients to colchicine was 150 (83.8%). The frequency of married patients was higher in the adherent group than the non-adherent group (72.4% vs. 47.3%, p = 0.013). The rate of the patients with comorbidities were 41.4% in the adherent group, whereas 22.0% in the non-adherent group (p=0.028). However, in terms of the type of comorbid disease, there was no statistically significant difference between groups. The median dose of colchicine was 1.5 (1.3-1.8) mg/day in the adherent group and 1.5 (1.0-1.5) mg/day in the non-adherent group (p=0.033). Considering age, gender, clinical manifestations, disease duration, socioeconomic or employment status, the place patient lived in, presence of proteinuria, chronic renal failure, and amyloidosis, resistance to colchicine, having a mutation on MEFV gene, a positive family history for FMF, there were no statistically significant differences between the adherent and non-adherent groups (p>0.05) (Table 2).

BMQ-T Specific Necessity scores were statistically significantly higher in the adherent group than the non-adherent group (p<0.001) (Table 3). Adherence with colchicine treatment has a positive correlation with the scores of BMQ-T Specific Necessity (r=0.495, p<0.001) (Table 4). BMQ-T General Overuse and General Harm scores were statistically significantly higher in the non-adherent group compared with the adherent group (p=0.003 and p=0.001, respectively) (Table 3). The correlations were negative between adherence to colchicine and the scores of BMQ-T General Overuse (r=-0.273, p< 0.001) and General Harm (r=-0.291, p<0.001) (Table 4).

4. Discussion

The mainstay of FMF treatment is colchicine, which increases the quality of life of the patients and prevents amyloidosis via decreasing the frequency and severity of febrile attacks. Disrupting colchicine use regarding various causes is an important issue due to the role of colchicine in preventing morbidity and mortality associated with FMF. Therefore, determining whether the patient is using colchicine in appropriate dose, the factors related to non-adherence to colchicine treatment and recommendations for solving the problems related to non-adherence come into prominence. The current study found out that most of the patients were non-adherent to colchicine, patients' thoughts about overusing colchicine and potential harm of colchicine. Having comorbidities and being married are factors increasing the adherence with colchicine. Ensuring the treatment adherence will accomplish treatment success and avoid misevaluation of colchicine resistance, decrease morbidity and mortality which may occur due to not using colchicine, and prevent unnecessary health care costs. To our knowledge, this is the first study to investigate adherence to colchicine treatment by using CQR and related factors in adult patients with FMF.

Previously, 5-15% of FMF patients revealed as non-responders to colchicine [5,13]. However, after excluding the patients who were non-adherent to colchicine, the prevalence of resistance was determined as approximately 5% [14]. In the current study, 11.7% of the patients accepted as colchicine resistant, which is higher than the reported rates in the literature. Considering the low ratio of colchicine adherence in our study group, it may be speculated that some colchicine resistant patients are actually non-adherent patients. Evaluating patients' adherence to the treatment is crucial for determining treatment response and planning future treatment options. Before the commencement of biological drugs, treatment adherence should be evaluated cautiously [10]. Adherence with a drug that has measurable blood levels (digoxin, valproic acid,

etc) or targets (hypouricemic agents, anti-diabetic agents, etc) can be determined more objectively. However, there is no laboratory assessment to measure the serum levels of colchicine. Therefore, colchicine adherence can only be assessed by patient-reported questionnaires. Morisky Green Levine Medication Adherence Scale is an option for the assessment of treatment adherence, but it does not give detailed information about the factors related to non-adherence of the treatment [15]. CQR is a questionnaire that is developed specifically for assessing compliance in rheumatologic diseases [11].

In the current study, the rate of the patients who were adherent to colchicine treatment was only 16.2%. In the literature, there was limited data regarding treatment adherence in patients with FMF and in general these studies used subjective reports of the patients, instead of relatively an objective scale or questionnaire. Ben-Chetrit reported fully adherence ratio of 13% in FMF patients [5]. A study performed among 96 FMF patients were found a adherence rate of 64.5% by asking the patients if they were using or not using the colchicine treatment [16]. Similar to this finding, in our study when the patients asked if they use colchicine regularly or not, 66.5% of the patients declared that they were using colchicine regularly which is a quite higher rate than detected with CQR. A feeling of guilt regarding being non-adherent may impel patients to hide the truth from the physicians. Additionally, CQR is a detailed questionnaire beyond evaluating taking the pills or not, but also, evaluates the factors related to non-adherence to the treatment, presence of a treatmet interruption, patient's belief about the benefit of the treatment and expectations from the treatment, and presence of the obstacles in receiving the treatment. Therefore, evaluating treatment adherence by using CQR may be more accurate both for the physician and the patient.

Recently, among children with FMF, an adherence rate of 30% was reported [17]. The higher rates among pediatric patients may be related to administering the drugs by their

parents. In another study evaluating the adherence rate among pediatric patients with FMF, the adherence rate was higher in younger patients [18]. Corsia et al. reported the adherence rate for colchicine treatment as 40% in the study group, whereas, in terms of adult and childhood patients, the adherence rates were 22% and 48%, respectively. On the other hand, Corsia et al. did not use any specific scale or questionnaire for evaluating the adherence rates [19].

In the current study, treatment adherence was better among patients with concomitant diseases than without concomitant diseases. Patients with concomitant diseases may have more concerns about the worsened outcomes of FMF. On the other hand, the type of concomitant disease did not differ between the groups. Patients with concomitant diseases may be more cautious about taking their treatment regularly. Also, adherent patients had higher doses of colchicine than non-adherent patients, according to the current study. The patients using higher doses of colchicine may have more severe disease, more frequent attacks, and also, these patients may have more concerns about the worsened outcomes of FMF. Also, they may have a low quality of life. The current study indicated that married patients were more adherent to treatment than unmarried patients. This situation may be associated with the assistance of the partner to take the pills regularly or due to increased sense of responsibility in married patients. Similarly, due to the administration of the drug by parents, the adherence rate was reported as 90.5% among patients under five years old [18]. Reminding (a partner, a parent, a phone alarm, or an application, vs.) may increase the adherence.

In patients who had developed amyloidosis due to FMF, colchicine still may effectively improve proteinuria and prevent progression to chronic renal failure [20]. Therefore, patients who had amyloidosis should continue using an appropriate dose of colchicine regularly. Ugurlu et al. reported a adherence rate of 33.3% in patients with FMF and

secondary amyloidosis [21]. A study that investigated the colchicine treatment adherence rate of FMF patients with amyloidosis showed that the patients had an adherence rate of 44%. Whereas, patients who had a diagnosis with amyloidosis simultaneously with FMF had an adherence rate of 93% [22]. In the current study, there was no relationship between the presence of amyloidosis and treatment adherence. Furthermore, the adherence rate is lower than the studies that assessed adherence in other rheumatologic diseases [12,23]. The rate of the patients, who were adherent to biological drugs, was 59.3% in rheumatoid arthritis, 62.5% in psoriatic arthritis and 76.2% in ankylosing spondylitis [24]. Xian et al. reported an adherence rate of 43.1% among systemic lupus erythematosus patients [25]. On the other hand, Yin et al. reported a rate of 9.6% adherence to urate-lowering therapy among patients with gout [26].

Early-onset of the disease and having a chronic course may lead to a decrease in treatment adherence in chronic diseases. Colchicine treatment should be life-length, and patients need to use pills two or three times a day. These may decrease the compatibility with colchicine treatment. Also, drug-related adverse events may be reasons for decreasing compatibility. In the current study, there was no association between adverse events related to colchicine and treatment adherence. Whereas, Sonmez et al. reported that pediatric patients with FMF who had more adverse events had lower rates of treatment adherence [18].

The treatment adherence of the patients with chronic diseases may influenced by psychosocial factors, concerns about side effects, unawareness of treatment requirement, patients' attitudes regarding their illness and beliefs about medicine. Approximately 40% of the patients with chronic diseases do not show adherence to treatment recommendations [27–29] Determining the attitudes and beliefs about

treatment is crucial for providing the adherence with the treatment. For this purpose, BMQ is a questionnaire designed to evaluate patients' perceptions and expectations about drugs. In the current study, according to BMQ-T and CQR scores, as the belief that colchicine is necessary increases, adherence increases. On the other hand, as the belief regarding colchicine overusing and harmfulness increases, adherence decreases. The relationship between beliefs and adherence indicates the importance of patient education for increasing treatment adherence . Also, providing better communication between physician and patient, informing patient regarding the adverse events of the drug, supplying a more sufficient social support may play role in increasing adherence to the treatment.

The current study had a few limitations. The physicological status of the patients may influence adherence with the treatment. The current study did not assess the depression or anxiety among the patients. Evaluating the presence of depression and anxiety may give more comprehensive information concerning non-adherence to colchicine. Also, evaluation of the quality of life may be beneficial for assessing the factors related to non-adherence. Finally, a prospective study design may give more comprehensive data about the reasons that have been increased adherence to the treatment.

In conclusion, non-adherence is not a rare issue among patients with FMF. Because being non-adherent to colchicine may raise worsened outcomes, physicians should emphasize to increase adherence in patient management. Also, evaluating treatment adherence in every visit should be kept in mind. Patients should be encouraged to be more adherent to colchicine to avoid worsened outcomes and increased need for using expensive treatment options.

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1 **Table 1. Sociodemographic and clinical characteristics of patients**

		Patients (n =179)
Age (years) *		30.0 (25.0-44.0)
Gender, n (%)	Male	113 (63.1)
	Female	66 (36.9)
Disease duration (years) *		15.0 (9.0-22.0)
Educational Status, n (%)	≤8 years	39 (21.8)
	9-11 years	29 (16.2)
	>11 years	111 (62.0)
Marital status, n (%)	Married	92 (51.4)
	Unmarried	87 (48.6)
Access to the treatment center, n (%)	Easy	147 (82.1)
	Difficult	32 (17.9)
Living place, n (%)	Rural	24 (13.4)
	Urban	155 (86.6)
Socioeconomic status, n (%)	Less than income	36 (20.1)
	Equal to income	124 (69.3)
	More than income	16 (10.6)
Employement status, n (%)	Employed	113 (63.1)
	Unemployed	66 (36.9)
Clinical manifestation, n (%)	Peritonitis	156 (87.2)

Fever	154 (86.0)
Arthralgia	104 (58.1)
Febrile myalgia	73 (40.8)
Arthritis	68 (38.0)
Pleuritis	63 (35.2)
Diarrhea	51 (28.5)
Erysipelas like erythema	42 (23.5)
Pericarditis	3 (1.7)
Orchitis	2 (1.8)
Presence of proteinuria, n (%)	25 (14.0)
Presence of amyloidosis, n (%)	8 (4.5)
Patients resistant to colchicine, n (%)	21(11.7)
Presence of MEFV gene mutations, n (%)	155 (91.7)
Patients with comorbidities, n (%)	45 (25.1)
Colchicine dose, (mg/day)*	1.5 (1.0-1.5)
*median (25th–75th percentile), MEFV: Mediterranean Fever	

Table 2. Relationships between sociodemographic and clinical characteristics of patients and CQR score

		CQR score		
		Adherence (≥80 %)	Non-adherence (< 80 %)	p-value
Patients, n (%)		29 (16.2)	150 (83.8)	
Age (years)*		37.0 (28.5-44.5)	29.0 (24.0-44.0)	0.099[a]
Gender, n (%)	Male	15 (51.7)	98 (65.3)	0.164[b]
	Female	14 (48.3)	52 (34.7)	
Educational Status, n (%)	≤8 years	7 (17.9)	32 (82.1)	0.641[b]
	9-11 years	3 (10.3)	26 (89.7)	
	>11 years	19 (17.1)	92 (82.9)	
Marital status, n (%)	Married	21 (72.4)	71 (47.3)	0.013[b]
	Unmarried	8 (27.6)	79 (52.7)	
Access to the treatment center, n (%)	Easy	25 (86.2)	122 (81.3)	0.372[b]
	Difficult	4 (13.8)	28 (18.7)	
Living place, n (%)	Rural	1 (3.4)	23 (15.3)	0.133[c]
	Urban	28 (96.6)	127 (84.7)	
Socioeconomic status, n (%)	Less than income	8 (22.2)	28 (77.8)	0.395[b]

	Equal to income	17 (13.7)	107 (86.3)	
	More than income	4 (21.1)	15 (78.9)	
Employement status, n (%)	Employed	15 (51.7)	98 (65.3)	0.164[b]
	Unemployed	14 (48.3)	52 (34.7)	
Presence of MEFV mutation, n (%)		22 (75.9)	133 (88.7)	0.992[b]
Presence of comorbidity, n (%)		12 (41.4)	33 (22.0)	0.028[b]
Colchicine dose(mg/day)*		1.5 (1.3-1.8)	1.5 (1.0-1.5)	0.033[a]

[a]Mann-Whitney U test, [b]Pearson Chi-Square test, [c]Fisher's Exact test

* median (25th–75th percentile),

CQR: Compliance Questionnaire on Rheumatology, MEFV: Mediterranean Fever

Table 3. Beliefs About Medicines Questionnaire scores in adherent and non-adherent patients

		CQR score			
	Overall (n=179)	Adherence ≥80 % (n=29)	Non-adherence < 80 % (n=150)	Z	p
BMQ-T Specific Necessity*	4.0 (3.4-4.6)	4.8 (4.1-5.0)	3.8 (3.35-4.25)	-5.260	<0.001
BMQ-T Specific Concerns*	2.8 (2.4-3.6)	2.8 (2.2-3.8)	2.8 (2.4-3.6)	-0.100	0.920
BMQ-T General Overuse*	2.5 (2.25-3.25)	2.25 (1.75-2.63)	2.75 (2.25-3.25)	-2.936	0.003
BMQ-T General Harm*	2.25 (2.0-3.0)	1.75 (1.38-2.63)	2.38 (2.0-3.0)	-3.212	0.001

Z=Mann-Whitney U test

* median (25^{th}–75^{th} percentile)

CQR: Compliance Questionnaire on Rheumatology, BMQ-T: Turkish translation of Beliefs About Medicines Questionnaire

Table 4. Correlation analysis between Beliefs About Medicines Questionnaire scores and Compliance Questionnaire on Rheumatology Scores

	CQR score	
	r	p
BMQ-T Specific Necessity*	0.495	<0.001
BMQ-T Specific Concerns*	-0.007	0.923
BMQ-T General Overuse*	-0.273	<0.001
BMQ-T General Harm*	-0.291	<0.001

r=Spearman correlation test

* median (25^{th}–75^{th} percentile)

CQR: Compliance Questionnaire on Rheumatology, BMQ-T: Turkish Beliefs About Medicines Questionnaire