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High prevalence of non-adherence to ulcerative colitis therapy in remission: knowing the problem to prevent loss

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ABSTRACT – Background – Ulcerative colitis (UC) is a chronic inflammatory disease whose manifestations can drastically affect the individual's quality of life, and therefore adherence to treatment is important in order to keep it in remission. **Objective –** To verify the prevalence of non-adherence and the influence of sociodemographic, clinical and pharmacotherapeutic characteristics associated with non-adherence to treatment of UC in remission. **Methods –** Cross-sectional study conducted with 90 individuals diagnosed with UC in remission. The information was collected through interviews during medical consultations at Medical Clinic of Gastroenterology of *Hospital Universitário da Universidade Federal de* Juiz *de Fora*. To verify the association of the variables under study with the outcome of interest and its measure of association, Student's *t*-test or Pearson's chi-square non-parametric test ($P<0.05$) was used and prevalence ratio and confidence interval were calculated. **Results –** A high prevalence of non-adherence (77.8%) was found among patients with UC in remission. The individuals most likely to not adhere to the treatment were those aged less than 50 years, who were not engaged in paid work, with high scores for anxiety and who used more than one medication as part of the treatment of UC. **Conclusion –** These findings reinforce that acknowledging the factors that influence the non-adherence behavior is of paramount importance for the development of strategies by health care professionals, assuring that those will be really effective to prolong, as much as possible, one of the most successful ways to maintain the UC remission period: the use of medications.

Keywords – Chronic disease; ulcerative colitis; drug therapy; proctocolitis; treatment adherence and compliance.

INTRODUCTION

Ulcerative colitis (UC) and proctocolitis are classified as a chronic, idiopathic inflammatory disease, characterized by recurrent inflammation of the intestinal mucosa that can extend from the rectum to the colon, causing diarrhea, rectal bleeding and other complications related to these primary symptoms[1]. It is a disease that affects men and women in the same proportion, in the age group of 30 to 40 years, causing an important limitation in these patients of working age[1,2].

The incidence of UC is increasing worldwide, with concern about the impact of Western lifestyle as a risk factor for the disease[3]. The number of diagnosed patients has been growing in countries in Europe and North America, as well as newly westernized countries in Asia, South America and the Middle East[3,4]. Specifically in Brazil, the same trend observed globally follows, with an increase in the prevalence of UC from 0.24/100,000 between 1986–1990 to 14.1/100,000 in 2014[5].

There is no cure for the disease and its treatment is chronic in order to induce and maintain remission of UC. The clinical remission is defined as the resolution of rectal bleeding and diarrhea, and endoscopic remission defined as a Mayo endoscopic subscore of 0 or 1[6]. Pharmacological options are chosen according to the severity of the disease, and aminosalicylates are considered as first-line for the treatment of mild to moderate UC[2,7,8].

For patients who do not respond to aminosalicylate monotherapy or with moderate to severe manifestations, the use of glucocorticoids and immunosuppressants to induce and/or maintain remission of symptoms should be included in the therapeutic regimen[8-10]. However, they all have limited beneficial effects and the risk of adverse reactions and side effects[11,12]. Despite this, adherence to treatment is essential to reach the state of remission, being thus considered a critical point in the management of patients with UC[13].

Non-adherence to treatment is considered a barrier for inducing remission and, therefore, for the patient's clinical improvement[13]. Multiple factors have been suggested to contribute to non-adherence in inflammatory bowel disease (IBD) including age, marital status, employment, gender, new patient status, duration of disease, multiple medications use, three times or more daily dosing, and comorbidities, but still varied form[14,15].

Adherence to drug treatment can be understood as the process by which patients take their medications as prescribed and it is composed of initiation, implementation and discontinuation. The patient is considered as non-adherent when is verified non-initiation of the prescribed treatment, sub-optimal implementation of the dosing regimen or early discontinuation of the treatment[16]. Thus,

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understanding individual barriers and adherence behaviors is critical for designing effective interventions to improve adherence. The objective of the present study was to verify the prevalence of non-adherence, as well as the influence of socio-demographic, clinical and pharmacotherapeutic factors in this behavior among patients with UC in remission that were seen at the Clinical Gastroenterology of *Hospital Universitário da Universidade Federal de Juiz de Fora* (HU-CAS UFJF).

METHODS

Scenario and study population

The study was conducted at the Medical Clinic of Gastroenterology of Center for IBD at HU-CAS UFJF. This service is considered a regional reference for specialized assistance and approximately 600 patients diagnosed with an IBD have benefited in 2018 from the service.

It was a cross-sectional, observational study, carried out between August 2017 and January 2018, a period that allowed all adult patients (>18 years old) of both genders with a diagnosis of UC made on the basis of routine clinical, radiological, endoscopic and histopathological criteria[17] to attend at least once for an outpatient consultation. At the time of the approach, the patient should be in a period of remission of the disease. To be classified as in clinical remission, a criterion used was that the individual should have a number ≤3 bowel movements per day, free of pus or blood, in addition to the absence of systemic symptoms[17].

Patients with UC who came for their routine appointments were asked to answer a semistructured questionnaire that started witha question about the activity status of their disease. If in remission, they were invited to proceed. Therefore, the following exclusion criteria were established: presenting active status of the disease, being on anti-TNF-α therapy, being in a period of pregnancy or lactation, and disinterest in participating in this research. Thus, 90 patients were considered eligible to participate.

This research was reviewed and approved by the Ethics Committee of the *Universidade Federal de Juiz de Fora*, MG Brazil (protocol number: 2.157.931).

Instruments and data analysis

The selected patients were invited to answer a semi-structured questionnaire so that the socioeconomic characteristics of each patient (age, gender, race, education level, occupation, marital status and region of residence) and personal history (smoking, alcoholism, comorbities, previous surgery in gastrointestinal tract, depression and anxiety) were evaluated.

Questions about clinical characteristics of UC and medications (anatomical extension of UC, time since diagnosis of UC, time in remission, time in clinical follow-up, acces to medications by public health system, total and kinds of medications and daily pills) presented in the same questionnaire that could not be answered by patients for some reason were later verified in their medical records.

The following instruments were used to collect the data: a questionnaire prepared by the authors of this article containing questions about socio-demographic aspects; the eight-item Morisky Medication Adherence Scale (MMAS-8)[18]; Beck depression inventory (BDI)[19]; and a depression and anxiety scale (Hopitalar Anxiety and Depression Scale - HADS-A)[20].

As in another study, we chose to group patients according scores in MMAS-8. Medium and low adherers (score <8) were grouped together and labelled them as MMAS-8 non adherers as there is neither a clear definition of medium and high adherence in the literature nor a clear clinical discrimination between the scores 6 to 8[18,21]. Anyway, scores <8 indicate failure in the following treatment. Thus, only those patients who presented 8 points on the MMAS-8 were considered as adherent to pharmacotherapy. The prevalence of non-adherence was calculated, therefore, by the number of non-adherent patients divided by the total population that participated in the study. For the assessment of depression and anxiety, scores ≥15 for BDI and ≥8 for HADS-A were considered relevant.

Statistical analysis was performed using GraphPad Prism 6.0 software. Quantitative variables were expressed as mean ± SD when normally distributed and significant differences between groups using Studen *t*-test were considered when $P<0.05$. Descriptive statistics of all relevant variables were calculated. All variables were dichotomized and then a descriptive analysis of the data was performed, presented in the form of tables of absolute and relative frequency. The association between variables under study with the outcome of interest was checked by Pearson's chi-square test (significance level of 5%) also being calculated prevalence ratio (PR) and 95% confidence interval (CI95%).

RESULTS

The epidemiological profile found for the population with UC in remission (n=90) showed gender equivalence (n=45, 50% male and n=45, 50% female), age 50.41±12.94 years, white (n=73, 81.1%), with some degree of literacy (n=87, 96.7%), engaged in paid activity (n=69, 76.7%), and married or in a consensual marriage (n=49, 54.4 %). The predominant region of residence, interestingly, was in cities neighboring the municipality where the outpatient service was offered (n=49, 54.4%). Comorbidities were present in 46 (51.1%) individuals, with no history of gastrointestinal surgery (n=87, 96.7%). The prevalence of depression and anxiety was 15.6% and 36.7%, respectively. The sociodemographic characteristics were described in table below (TABLE 1).

The prevalence of non-adherence in the sample was 77.8% and the socio-demographic variables that were related to the non-adherence behavior were age (between 18 and 50 years, 48.2±1.5 years) and not being engaged in paid activity, observing that younger individuals and those who were not engaged in paid activity were, respectively, 2.6 and 5.5 times more likely to show non-adherence behavior. In addition, it was observed that anxiety also was a factor that increased the chance of this behavior by 3.3 times.

With regards to general clinical features of UC, no characteristics were found to interfere with non-adherence behavior. There was a great variation in the times of diagnosis, period in remission and time of follow-up at the clinic. Regarding the anatomical extent of inflammation, cases of panconlitis predominated (46.7%, n=42). These data are described in TABLE 2.

The analysis of the pharmacotherapy aspects showed the most prescribed medication was mesalazine (5-ASA) (54.4%). The number of medications used influenced the non-adherence behavior, and those who used only one type of medication were more adherent than those who used two or more types ($P=0.041$). The quantity of daily pills and daily dosage did not influence in non-adherence behaviour ($P=0.11$ and $P=0.48$, respectivaly). There was a predominance of free supply of medications through the public health system, however this aspect was not relevant in adherence behaviour ($P=0.316$) (TABLE 3).

TABLE 1. Distribution of patients with UC in remission according to sociodemographics characteristics.

Sociodemographic characteristics	Adherence		Total	PR (CI)	*P*
	Yes (n=20)	No (n=70)			
Age (years) (mean±SD)	58.2±2.3	48.2±1.5	-	-	0.002#
Distribution by age group					
18-50 years	6 (6.7%)	41 (45.6%)	47 (52.2%)	2.6 (1.121–5.983)	0.04*
>50 years	14 (15.6%)	29 (32.2%)	43 (47.8%)		
Gender					
Female	8 (8.9%)	37 (41.1%)	45 (50%)	-	0.44
Male	12 (13.3%)	33 (36.7%)	45 (50%)		
Race					
White	17 (18.9%)	56 (62.2%)	73 (81.1%)	-	0.86
Non-white	3 (3.3%)	14 (15.6%)	17 (18.9%)		
Education level					
Illiterate	1 (1.1%)	2 (2.2%)	3 (3.3%)	-	0.81
Literate	19 (21.1%)	68 (75.6%)	87 (96.7%)		
Occupation					
In activity (formal or informal employement)	13 (14.4%)	14 (15.6%)	27 (30%)	4.3 (1.986–9.523)	0.0002*
No activity (unemployed or retired)	7 (7.8%)	56 (62.2%)	63 (70%)		
Marital status					
Single	6 (6.7%)	35 (38.9%)	41 (45.6%)	-	0.18
Married/consensual marriage	14 (14.4%)	35 (38.9%)	49 (54.4%)		
Region of residence					
Juiz de Fora	7 (7.8%)	34 (37.8%)	41 (45.6%)	-	0.41
Neighboring cities	13 (14.4%)	36 (40%)	49 (54.4%)		
Smoking					
Yes	1 (1.1%)	7 (7.8%)	8 (9.9%)	-	0.80
No	19 (21.1%)	63 (70%)			
Alcoholism					
Yes	1 (1.1)	2 (2.2%)	3 (3.3%)	-	0.81
No	19 (21.1%)	68 (75.6%)	87 (96.7%)		
Comorbities					
Yes	12 (13.3%)	34 (37.8%)	46 (51.1%)	-	0.52
No	8 (8.9%)	36 (40%)	24 (26.7%)		
Previous surgery in gastrointestinal tract					
Yes	1 (1.1)	2 (2.2%)	3 (3.3%)	-	0.81
No	19 (21.1%)	68 (75.6%)	87 (96.7%)		
Depression					
Yes	4 (4.4%)	10 (11.1%)	14 (15.6%)	-	0.79
No	16 (17.8%)	60 (66.7%)	76 (84.4%)		
Anxiety					
Yes	5 (5.5%)	42 (46.7%)	47 (52.2%)	3.3 (1.371–8.150)	0.01*
No	15 (16.7%)	28 (31.1%)	43 (47.8%)		

PR: prevalence ratio; CI: confidence interval; UC: ulcerative colitis. #*P*: significant value for Student test-*t*; **P*: significant value for Pearson's chi-square test.

TABLE 2. Distribution of patients with UC in remission according to clinical characteristics.

Clinical characteristics	Adherents patients (n=20)	Non-adherents patients (n=70)	Total sample (n=90)	*P*
Anatomical extension of ulcerative colitis				
Pancolitis	9 (10%)	33 (36.7%)	42 (46.7%)	0.99
Other	11 (12.2%)	37 (41.1%)	48 (53.3%)	
Diagnosis of the disease (months)				
Up to 10 years	12 (13.3%)	37 (41.1%)	49 (54.4%)	0.61
>10 years	8 (8.9%)	33 (36.7%)	41 (45.6%)	
Time in remission (months)				
Up to 3 years	7 (7.8%)	34 (37.8%)	41 (45.6%)	0.42
>3 years	13 (14.4%)	36 (40%)	49 (54.4%)	
Time in clinical follow-up				
Up to 7 years	14 (15.6%)	54 (60%)	68 (75.6%)	0.56
>7 years	6 (6.7%)	16 (17.8%)	22 (24.4%)	

**P*: significant value for Pearson's chi-square test. UC: ulcerative colitis.

TABLE 3. Distribution of patients with UC in remission according to clinical characteristics.

Pharmacotherapeutic characteristics	Adhesion		Total sample (n=90)	PR (CI**)	*P*
	Yes (n=20)	No (n=70)			
Total access to medications by Public Health System					
Yes	19 (17.1%)	58 (52.2%)	77		0.32
No	1 (1.1%)	12 (13.3%)	13 (14.4%)		
Total of medications					
One medication	15 (16.7%)	31 (34.4%)	46 (51.1%)	2.9 (1.202–7.144)	0.02*
More than one medication	5 (5.6%)	39 (43.3%)	44 (48.9%)		
Kinds of medications***					
Azatioprine	7 (7.8%)	27 (30.0%)	34 (37.8%)		0.80
Glycocorticoid	2 (2.2%)	10 (11.1%)	12 (13.3%)		0.72
Mesalazine	11 (12.2%)	38 (42.2%)	49 (54.4%)		>0.99
Sulfasalazine	7 (7.8%)	28 (31.1%)	35 (38.9%)		0.62
Daily pills (mean, range)					
Up to five pills/day	14 (15.6%)	32 (35.6%)	46 (51.1%)	-	0.07
More than 5	6 (6.7%)	38 (42.2%)	44 (48.9%)		

**P*: significant value for Pearson's chi-square test. UC: ulcerative colitis. **CI: confidence interval; PR: prevalence ratio. ***The chi-square test was done with each class compared to the class 'others'. A patient could be using more than one drug class.

DISCUSSION

RCU is a chronic condition requiring lifelong medication to minimize the incidence of symptomatic recurrences, need of surgery, hospitalization and several issues such as colorectal cancer[10]. Nevertheless, a large proportion of patients are non-adherent to their prescribed therapeutic regimen as demonstrated by this study, which found a high non-adherence prevalence (77.8%). Other investigations with Brazilian populations showed high non-adherence prevalence (63.3%) of a similar way to what we found among patients with UC in remission[22]. This issue has also been demonstrated for Chron disease, although with a slightly lower prevalence[22,23]. The quality of life of patients affected by UC can be severely impaired during phases of active disease but often returns to normal levels during remission, hence the importance of patients staying adherent to therapy[13,24].

Some common demographic variables such as age, marital status, living alone, gender, race, income, occupation, number of dependents, level of education or personality type have been the subject of controversial statements about their impact on non-adherence behavior in different treatments for chronic diseases[15,25]. In this study, however, out of the twenty one variables analyzed, only four were found to be related to non-adherence behavior: age, occupation, anxiety and quantity of medications used.

Increasing age, for example, has already been associated with low adherence to some treatments, such as arterial hypertension[26]. In contrast, in our data as well as in other studies on UC[10,27], younger patients demonstrated a lower degree of adherence and this may be a peculiarity of this type of chronic disease[20,28]. In this study, the medium age of non-adherents patients (48.2±1.5 years) was lower than adherents (58.2±2.3 years) and this finding is in agreement to described by D'Inca et al.[28] and De Castro et al.[19] in non-active IBD outpatients.

The portion of the sample individuals identified as having anxiety was highlighted in this study. In another survey involving patients with IBD, a frequency of 24.4 to 31.9% of anxiety in these patients was estimated[29], while our findings pointed to 36.7% of individuals with this disorder. According to Choi et al., the appearance of disorders such as anxiety and depression is related to the status of having a chronic disease diagnosis, but also to several individual circumstances[30] - which may include lack of exercise and being engaged in paid activity, a factor associated with low adherence in the sample. However, such comorbidities can also result from the use of some drugs and, in this case, especially glucocorticoids[30]. In general, anxiety can worsen the manifestations of UC and, as shown, be associated with non-adherence behavior.

As already demonstrated, the impact of these factors can produce different results according to the patients in question. Thus, the most assertive way to deal with non-adherence in a specific population is through in-depth knowledge of how much they can be affected by these variables[25,31].

Other complementary criteria for sociodemographic, clinical and pharmacotherapy features were investigated but also had not been associated with this issue. Our results were similar to Cornelio et al., who investigated risk factors to non-adherence to therapy in Chron's disease patients, without significant findings[23].

There are many reasons for not adhering to medical recommendations; however, some of them are directly related to the choice of an appropriate therapy. The ineffectiveness, the low quality of life of the patient and the high cost of therapy are also negative influences for adherence[32], although they are absent in this study sample. Within the group in question, adherence was achieved demonstrating the effectiveness of the treatment, mostly obtained due to the public health service being free of charge and by significantly improving these individuals' quality of life.

On the other hand, both the occurrence and the fear of side effects also impair adherence. The remission phase, especially, can encourage the belief that potential risks related to the medications surpass the need to maintain their use, since the patients perceive themselves as free from their long-term symptoms[33]. Some medications used for IBD have been associated with a non-adherent behavior to therapy. So, we hypothesized that the possibility of adverse events related to long-term use of medications, even without symptoms of active disease, may be a strong influence on the abandonment or noncompliance of therapy in this sample.

For this reason, an important role is played by the assistant physician that, when planning pharmacological treatment, must select drugs with the utmost care to eliminate risk factors that may contribute to therapeutic failure and encourage the patient to actively participate in the entire process[31,32]. It was realized that using more than one type of medication contributes to non-adherence and, whenever possible, treatments with drug combinations should be reduced in length as much as possible. Although it did not reach statistical significance, consuming more than five pills daily indicated a trend towards possible non-adherence behavior. Alternatives must be considered by the medical team aiming such reduction.

Regarding the limitations of this investigation, it should be noted that the present study did not focus on assessing the quality and the understanding of the information received about the treatment from the patient's perspective. Thus, the knowledge about health literacy of this group is an important point to be considered for future investigations. On this subject, it has already been mentioned that low levels of cooperation and adherence can also result from the action of health care providers. In this case, the perception that the patient has that they are not receiving attention for a long enough period, the lack of intensification of therapy, long waiting times for consultations and the absence of adequate communication between health care providers and the patient must be emphasized[34].

In addition, despite the fact that MMAS-8 has been established with excellent validity and reliability in patients with chronic diseases[21] and also as the first validated compliance scale in IBD, there are still conflicting data on its performance in such patients[35,36]. Thus, it is suggested that more specific studies be carried out with different populations affected by UC, including the use of other tools to measure adherence, such as screening the drug metabolite or counting pills. Using self-report as a method of assessing adherence is simple, inexpensive and useful in clinical practice, but tends to overestimate patient compliance. The combination of different methods increases the measurement's accuracy[37].

Based on the analyzed data, the present study identified that high proportions of patients with UC in remission presented non-adherence behavior to therapy. Patients over 50 years old, who were not engaged in paid activity, with symptoms of anxiety and who used more than one type of medication were identified as having the highest risk for non-adherence behavior among UC patients in remission.

These findings reinforce that acknowledging the factors that influence the non-adherence behavior is of paramount importance for the development of strategies by health care professionals, assuring that those will be really effective to prolong, as much as possible, one of the most successful ways to maintain the UC remission period: the use of medications.

Authors' contribution

Franco FCZ: data's colect and text writer; Oliveira MCC: text writer. Gaburri PD: text writer and review; Franco DCZ: data analyse, text writer and review; Chebli JMF: Research conductor and final review.

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Franco FCZ, Oliveira MCC, Gaburri PD, Franco DCZ, Chebli JMF. Elevada prevalência de não adesão ao tratamento da colite ulcerativa em remissão: conhecer o problema para prevenir o prejuízo. Arq Gastroenterol. 2022;59(1):40-6.

RESUMO – Contexto – Colite ulcerativa é uma doença inflamatória crônica que pode apresentar manifestações graves que afetam drasticamente a qualidade de vida do indivíduo e, dessa maneira, a adesão ao tratamento é importante a fim de manter a doença em remissão. **Objetivo –** Verificar a prevalência de não adesão e a influência de características sociodemográficas, clínicas e farmacoterapêuticas associadas a não adesão ao tratamento da colite ulcerativa em remissão. **Métodos –** Estudo transversal envolvendo 90 indivíduos diagnosticados com colite ulcerativa em remissão. As entrevistas foram conduzidas durante as consultas médicas realizadas na Clínica Médica de Gastroenterologia do Hospital Universitário da Universidade Federal de Juiz de Fora. Para verificar a associação entre as variáveis com o desfecho de interesse, foi aplicado teste-*t* de Student ou teste não-paramétrico qui-quadrado de Pearson ($P<0,05$) e também razão de prevelência e intervalos de confiança foram calculados. **Resultados –** Uma elevada prevalência de não adesão (77,8%) foi encontrada dentre os pacientes com colite ulcerativa em remissão. Os indivíduos mais propensos ao comportamento em questão foram aqueles com menos de 50 anos, sem trabalho remumerado, com escores mais elevados no teste de ansiedade e que utilizavam mais de um medicamento para o tratamento da colite ulcerativa. **Conclusão –** Estes achados reforçam que o conhecimento de fatores que influenciam o comportamento de não adesão é de grande importância para o desenvolvimento de estratégias para a equipe de saúde, garantindo que estas sejam realmente eficazes para prolongar, tanto quanto possível, uma das formas mais bem-sucedidas de manter o período de remissão da colite ulcerativa: o uso de medicamentos.

Palavras-chave – Doença crônica; colite ulcerativa; terapia medicamentosa; proctocolite; adesão e adesão ao tratamento.

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