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Original Article

Factors Affecting Non-adherence to Medications in Patients with Inflammatory Bowel Disease-Ulcerative Colitis

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ABSTRACT

Background / Aim: Non-adherence to treatment is an important determinant of relapses and complications in Inflammatory bowel disease-ulcerative colitis (IBD-UC). We assessed the adherence to treatment advised in IBD-UC and reasons for non-adherence in tertiary government hospital.

Methods: This cross-sectional study included patients with histologically confirmed IBD-UC admitted indoor as well as those visiting outdoors between December 2020 and August 2023. Non-adherence to treatment was assessed on the basis on questionnaire and defined as medicine intake less than 80% in last two weeks.

Results: A total of 178 participants completed the questionnaire, mean age (34.17±12.3 years), average disease duration was 3.47±2.7 years, and 56 (31.5%) patients were adherent to treatment. The adherence to oral mesalamine, salfasalazine, azathioprine, oral prednisolone, tofacitinib and topical mesalamine were 38.2%, 31.3%, 66.7%, 77.8%, 83.3% and 33.3% respectively. 78 patients were receiving treatment free-of-cost, among them 31 (39.7%) were adherent. The primary reasons for non-adherence among patients were cost and unavailability (33.1%), feeling better without medications (22.9%) and forgetfulness (12.7%). Univariate analysis revealed significant association of adherence with satisfaction (p=0.001), number of hospital visits (p=0.001) and disease awareness (p=0.014). Factors such as demographics, disease characteristics and bearing treatment-cost showed no statistically significant association. Regression analysis identified patient-satisfaction as the sole predictor of medication adherence (p = 0.001).

Conclusion: One-third of patients with UC adhered to medication regimens. Adherence was significantly associated with patient satisfaction, number of hospital visits and disease awareness while education, socioeconomic status, and disease characteristics showed no association. Free-of-cost treatment did not make a difference in adherence.

KEYWORDS: Inflammatory bowel disease, Ulcerative colitis, Adherence, Non-adherence.

Introduction

Inflammatory bowel disease- ulcerative colitis (IBD-UC) is a chronic and relapsing disease that usually requires lifelong treatment. The treatment often requires frequent dosing, multiple pills per day, inconvenient administration methods such as enemas and infusions. Additionally, it imposes financial burden on the health care along with the possibility of adverse effects. Non-adherence to these prescribed treatment regimens has emerged as a significant factor contributing to the recurrence of IBD symptoms.[1] Worldwide, many studies on IBD patients have revealed significant non adherence. However, the rates of adherence in studies exhibited significant heterogeneity based on factors such as the demographic composition of study participants (distinguishing between adults and pediatric patients), the chosen method of administration, and the diverse approaches employed for measuring adherence (including blood analysis, pharmacy refill records, and self-report methods such as diaries, interviews, and questionnaires). A comprehensive systematic review encompassing 17 studies comprising a total of 4,322 adult subjects with IBD revealed non-adherence rates to oral medications ranging from 7% to 72%.[2]

Non-adherence to prescribed treatment regimen is associated with increased risk of relapses in individuals with IBD, leading to a deterioration in their quality of life and imposing increased social and personal costs.[1,3,4,5] Factors influencing adherence in IBD patients including demographics, clinical aspects, psychosocial elements, and cost of treatment have been explored in multiple studies.[1,3,5-16]

Previous studies from India examined the relationship between a variety of factors and medication non-adherence and showed contrasting results. Percentage adherence in one study being 82.4%, while in another, it was only 19%.[5-6] One of the studies concluded that higher education status, professional occupation and upper socioeconomic status were predictors of non -adherence.[6] However, factors such as inconvenient drug administration, distance from the drug distribution centre, and satisfaction with treatment advice on drug adherence have not been addressed. Cost of treatment may be an important factor affecting adherence as drugs in IBD are expensive. Under Government Schemes, free treatment is available only at few centers in India. Enhancing medication adherence presents a significant challenge for healthcare providers treating individuals with IBD.

In this study, we aimed to identify adherence and reasons for non-adherence in a government-funded Tertiary Care Hospital.

Methods

Study Design and Population: This cross-sectional study was conducted at the Gastroenterology Department, SMS Medical College, Jaipur in patients with histologically confirmed ulcerative colitis admitted inpatient / wards as well as those visiting outpatient clinics between December 2020 and August 2023. Newly diagnosed patients (diagnosed within the past 2 months) and those who did not give consent or were unable to answer the questionnaire were excluded. A printed simple proforma questionnaire was prepared that included personal and socio-demographic profiles, disease characteristics (from previous treatment records) and number of hospital visits in last 12 months of study subjects. The socio-demographic characteristics were defined according to modified Kuppuswamy socioeconomic scale for the year 2022. The direct expenditure of patients for treatment, including physician consultation and hospitalization, was free for all patients. Laboratory investigations, diagnostic procedures, and prescription drugs were free of cost for a select group of patients while subsidized for others. The questionnaire needed information (based on recall from the previous 2 weeks) on the intake of prescribed medication, frequency of missed doses and reason for non-adherence to prescribed medications. Non-adherence to treatment was defined as medication intake < 80% of the dose advised.[1] The patients' recall of medicine intake in the last 2 weeks was used to calculate non-adherence.[5] Patient satisfaction was assessed by Visual Analogue Scale (VAS) and scored from 0 to 100 point with extremes of satisfaction at either ends and a cut-off of 50 point was taken for satisfaction. Awareness about disease was assessed based on the patient knowledge about need of lifelong treatment and importance of adherence. The study received institute's ethics committee approval prior to enrollment. Written informed consent was obtained from each patient.

Statistical Analysis: The data was initially entered into Microsoft Excel. Nominal and categorical variables were summarized using frequencies and percentages, while continuous variables were summarized using mean and standard deviation. Proportional significance testing was conducted through the analysis of proportions using the Z test and the univariate analysis using chi-square test. A p value of ≤ 0.05 was considered statistically significant. Regression analysis was done to study the factors affecting adherence. Regression analysis was performed using linear regression where the dependent variable was a continuous variable, and multiple regression if the dependent variable was a categorical variable. Significance value / p value for independent variables was reported and those less than 0.05 were considered as significant variables affecting the dependent variable. All statistical analyses were performed using SPSS version 12, IBM software. To calculate the adherence rate, the following formula was used:

Percentage of adherence of drug (in %) = (Number of dose taken)/(Number of doses prescribed in 2 weeks period) x 100

The resulting percentage of adherence ranged from 0 to 100%.

Results

One hundred eighty-six patients with ulcerative colitis (UC) were initially screened. However, eight patients were excluded because they had been newly diagnosed within the past two months. Out of the remaining 178 patients, gender distribution was nearly equal comprising 93 (52.2%) males and 85 (47.8%) females. Mean age of participants at the time of recruitment and diagnosis was 34.1±12.3 years and 29.8 ±11.9 years, respectively. Most patients were unemployed and belonged to lower socioeconomic strata. Mean duration of disease was 3.4 ± 2.7 years. The majority of patients, 131 (73.6%), exhibited left-sided colitis or proctitis, 20 (11.2%) had pancolitis, and 27 (15.2%) had an unknown extent of the disease. None of the study patients had undergone surgery for IBD. 87 (48.9%) patients were in remission. The mean number of relapses was 2.04 ± 1.1 (**Table 1**).

The mean number of hospital visits in one year was 7.08±3.9. Regarding cost of treatment, 78(43.8%) patients availed free treatment, and 98 (54%) paid for their treatment.

In our study 1/3rd of patients- 56 (31.5%) adhered to their prescribed treatment. Among the prescribed medications, oral mesalamine was prescribed in 159 patients; however, only 68 (38.2%) patients demonstrated adherence. 16 patients were on sulfasalazine, out of which 5 (31.3%) adhered to the treatment. For oral prednisone, prescribed in 29 of patients, 21 (77.8%) exhibited adherence. Oral azathioprine was prescribed to 51 patients and 34 (66.7%) exhibited adherence. Oral tofacitinib, was prescribed for only 6 patients, and 5 (83.3%) of them were adherent. Topical ASA was prescribed to 48 patients, and 16(33.3%) of them were adherent.106 patients were on multiple drugs. None of our patients were on biologicals. A total of 141 (79.2%) out of 178 patients were satisfied with their treatment.

Table 1: Personal and sociodemographic profile of the study subjects and disease characteristics.

		n=178 Mean±SD or Percentage
Age	(Mean ± SD)	34.17± 12.32
Gender	Male	93 (52.2)
	Female	85 (47.8)
Socioeconomic status	Upper	22 (12.6)
	Upper middle	50 (28.6)
	Lower middle	32 (18)
	Upper lower	40 (22.8)
	Lower	32 (18)
Disease characteristics		
Age at diagnosis (years)	Mean ±SD	29.88±11.9
Duration of Disease	Mean ± (SD)	3.47 (±2.7)
Extent of disease	Proctitis	30 (16.9)
	Left sided colitis	101 (56.7)
	Pan colitis	20 (11.2)
	Not known	27 (15.2)
Disease activity	Remission	87 (48.9)
	Active disease	91 (51.1)
Cost of treatment	Government scheme	80 (46)
	Self	98 (54)

The primary reasons for non-adherence to medications among the patients in the study were diverse. The most cited reasons included the cost or unavailability of medications, reported by 39 (33.1%) patients. Of non-adherent patients, 27 (22.9%), indicated that they felt better without medications, while 15 patients (12.7%) reported forgetfulness as a contributing factor. 11 out of 32 patients non-adherent to topical ASA cited inconvenient routes of drug administration as a reason for non-adherence (34%). Other reasons for non-adherence included the perception of lifelong treatment, seeking alternative treatments, experiencing adverse drug events and frequent drug dosing in decreasing frequency. (**Table 2**)

Out of the 80 patients who received free treatment, 31 (39.7%) were adherent, whereas among the 98 patients who bore the cost of their treatment, 25 (25.5%) adhered to the prescribed treatment regimen.

Univariate analysis of factors influencing medication adherence suggested significant relation to patient satisfaction ($p = 0.001$), disease awareness ($p = 0.014$) and frequency of hospital visits in the last year ($p = 0.001$). On the other hand, our analysis revealed that factors such as age, sex, rural or urban residence, education, socioeconomic status, age of onset, disease duration, extent of the disease and disease activity did not show statistically significant difference. Other factors, such as the distance from the drug distribution center, the use of multiple drugs and the addition of topical agents did not demonstrate statistically significant associations with medication adherence. The difference in adherence between patients who availed free treatment and those who bore treatment cost was not statistically significant ($p = 0.082$). However, regression analysis highlighted that, among these factors, patient satisfaction with treatment remained the sole statistically significant predictor of compliance ($p = 0.001$). (**Table 3**)

Table 2: Adherence rate and reason for non-adherence in study subjects.

		N (Percentage)	Percentage adherence
Adherence rate	Mesalamine	159 (89.3)	38.2
	Sulfasalazine	16 (8.9)	31.3
	Oral steroid	29 (16.3)	77
	Azathioprine	51 (28.7)	66.7
	Tofacitinib	6 (3.4)	83.3
	Local 5-ASA	48 (27)	33.3
	More than one drugs	106 (59.5)	32
	Overall Adherent	56	31.5%
	Overall non-adherent	122	68.5%
Reason for non-adherence	Forgetting dose	15	12.2%
	Lifelong treatment	2	1.6%
	Frequent dosing/timing	4	3.2%
	Inconvenient route of drug administration	11	9.0%
	Alternative treatment	10	3.70%
	Job/ occupation	1	0.8%
	Cost or unavailability of medication	39	31.9%
	Felt better without medication.	27	22.9%
	Adverse effects of medication	5	6.1%

Discussion

Maintaining drug adherence is of paramount importance for effectively managing chronic conditions such as IBD-ulcerative colitis (UC). It demands continuous monitoring to ensure treatment support and adherence.

Non-adherence has been associated with an increased risk of relapse, adverse outcomes such as reduced quality of life, missed workdays, poor pregnancy outcomes, and even colorectal cancer.[1,17-24] Moreover, it significantly escalates healthcare costs.[25] Thus, recognizing and addressing non-adherence is essential to enhance patient outcomes and alleviate economic burdens. In this study, involving 178 patients (mean age 34 year, 52% males) with ulcerative colitis (UC), we observed that patient demographics and disease characteristics varied considerably. Notably, a substantial portion of patients (68.5%) exhibited non-adherence with prescribed medications, with reasons ranging from cost or unavailability of medicines to "felt better without treatment". Worldwide, studies on IBD patients revealed significant non-adherence trends. In a multicenter study from Argentina, 50.3% of patients reported inadequate adherence to oral medications; another study from the Czech Republic found that 32% reported intentional non-adherence, with 42% reporting unintentional.[26-27]

Table 3: Predictor of non-adherence in patients with ulcerative colitis Regression analysis.

Variable	Adherent (n=56)	Non-adherent (n=122)	p-value
Age	33.73 ±11.60	34.38 ±12.68	0.747
Duration of disease	3.88 ± 3.49	3.28 ±2.37	0.184
Age of onset	29.20 ± 11.23	30.02 ±12.31	0.672
Number of Relapses	2.29 ±1.12	1.93 ±1.10	0.460
Number of Hospitalizations	0.84 ±1.63	0.61 ±1.47	0.347
Number of Hospital visit in 1 Yr	9.43 ±2.99	6.01 ±3.81	0.001
Sex			
Male	33/56 (58.92%)	60/122 (49.18%)	0.227
Female	23/56 (41.08)	62/122 (50.82%)	
Area			
Urban	22/56 (39.28%)	60/122 (49.18%)	0.219
Rural	34/56 (60.71%)	62/122 (50.82%)	
Education			
Illiterate and primary education	9/56 (16.08%)	34/122 (27.86%)	0.088
Middle school or higher education	47/56 (83.92%)	88/122 (71.14%)	
Socioeconomic status			
Lower economic status	3/56 (5.35%)	8/122 (6.55%)	0.757
Upper Lower or higher Socioeconomic status	53/56 (94.64%)	114/122 (93.45%)	
Extent of disease			
E1	11/56 (19.64%)	19/122 (15.57%)	0.674
E2	28/56 (50%)	73/122 (59.83%)	
E3	7/56 (12.50%)	13/122 (10.65%)	
Unknown	10/56 (17.85%)	17/122 (13.94%)	
Disease activity			
Remission	30/56 (53.57%)	57/122 (46.72%)	0.396
Relapse	26/56 (46.43%)	65/122 (53.28%)	
Disease Awareness			
Yes	49/56 (87.50%)	86/122 (70.49%)	0.014
No	7/56 (12.50%)	36/122 (29.51%)	
Satisfaction to treatment			
Yes	54/56(96.42%)	87/122 (71.31%)	0.001
No	2/56(3.58%)	35/122 (28.69%)	
Topical Therapy on non-adherence			
Yes	10/56 (17.85%)	38/122 (31.14%)	
No	46/56 (82.15%)	84/122 (68.86%)	0.640
Distance from Drug distribution centre	175.98 ±134.52	165.77 ±303.35	0.820
Mode of payment for treatment			
Government scheme	31/56 (55.35%)	49/122 (41.1%)	0.082
Self	25/56 (44.65%)	73/122 (59.90)	

The documented rates of medication non-adherence among Asian patients with inflammatory bowel disease (IBD) falls within the range of 20% to 30%.[28-29] In earlier Indian studies, Tomar SK et al. from Delhi, found that 82.4% of patients with ulcerative colitis patients were adherent with therapy.[6] In another study by Jay Bhatt et al from Mumbai, 19% of the patients with IBD (ulcerative colitis and Crohn's disease) were adherent with therapy.[5] Compared to the above studies, we included only patients with ulcerative colitis, resulting in a more homogenous population. The adherence rate in our study was 31.5%. If we reduce the diagnostic threshold of adherence to more than 60% of total advised dose (in contrast to pre-defined 80%) then adherence in the study by Jay Bhatt et al would be 87.4%, while in our study, it would have been 50%.[5] (**Table 4**). In our study, patients on oral steroids, azathioprine and tofacitinib were more adherent, highlighting that having extensive disease or having frequent relapses that led to the use of these drugs, resulted in improved adherence; this is in compliance with study by Tomar SK et al. where adherence to steroids (100%) was more than overall adherence rate (82.4%).

Common reasons for non-adherence in the study by Tomar SK et al. were forgetting doses (19.6%), unavailability of medications (13.2%), "feeling better without medications" (12.7%), and side/adverse effects (4.9%) whereas in the study by Jay Bhatt et al, the main reasons for non-adherence were forgetfulness (77%), feeling better (14.17%), high frequency of doses (10.1%), and no effect of medications (7.87%).[5-6] In our study, we found that common reasons for non-adherence included the cost or unavailability of medications (33.1%), feeling better without medications (22.9%), and forgetfulness (12.7%), which is in sharp contrast to study by Jay Bhatt et al, possibly owing to increased availability of sustained release tablets.

World-wide, numerous studies have identified diverse predictors of non-adherence. In a Korean study non-adherence was associated with younger age, longer outpatient intervals and limited medication knowledge, this is in concordance with our study that awareness about disease and regular follow up are important determinants of adherence.[30]

In a Spanish study, forgetfulness, feeling better, feeling worse, carelessness, long-standing IBD, inadequate knowledge, high depression scores, patient-physician discordance were predictors of non-adherence.[31] A study from Italy related non-adherence with disease duration, significant association with forgetfulness, feeling better, feeling worse, frequent dosing, topical therapy.[35] In all these studies feeling better on treatment is important contributor for non adherence.

Table 4: Percentage adherence to any drugs.

% Adherent to any drug	Number of patients (n=178)
0-20%	24
21-40%	26
41-60%	40
61-80%	42
81-100%	46

A Belgian Study in 2016 revealed age younger than 40 years, higher education, unmarried status and mesalamine use as predictors of non-adherence while self-employment as protective.[32]

In a study from Prague, non-adherence was associated with higher education, medication side effects while factors associated with adherence were older age. Non-adherent patients more likely had chronically active or relapsed disease state.[33]

Our statistical analysis revealed compelling associations between adherence and specific factors emphasizing the significant impact of patient satisfaction, hospital visit frequency, and awareness about the disease on adherence behavior. In the study by Tomar SK et al, patient's level of education ($p<0.001$), occupation ($p=0.097$), and socioeconomic status ($p=0.021$) exhibited an inverse correlation with adherence.[6] Interestingly, individuals in higher socioeconomic brackets with professional educational and occupational backgrounds demonstrated the lowest adherence rate (47%). Conversely, patients from lower socioeconomic strata, characterized by lower educational attainment and unemployment, displayed the highest adherence rate (100%). In our study, patient education ($p=0.875$) and socioeconomic status ($p=0.735$) did not show a significant association with non-adherence.

Our study investigated the impact of drug administration routes on patients' adherence. Among the 48 patients receiving topical ASA, 16 (33.3%) adhered to

treatment prescribed, while 11 out of 32 adherent patients cited inconvenience to drug administration as primary reason for non-adherence. This aligns with previous study by Prantera et al (a randomized controlled trial) that demonstrated higher adherence rates with oral 5-ASA compared to topical 5ASA (97.0% vs. 87.5%). D'Incà et al., also demonstrated in their real-world study that, there is increased non-adherence with rectal therapy compared to oral therapy (68% vs. 40%, p=0.001), mainly due to patients' discomfort and administration inconvenience.[34-35]

In our study population, some of the direct expenditures of treatment, including physician consultation and hospitalization, were free of cost. Other expenditures, including prescription drugs for a limited period, laboratory investigations, and diagnostic procedures were either subsidized or free under the Government Scheme. Apart from these, the indirect cost, including logistics and loss of workdays plays an important role, as most of our patients belonged to remote areas. Nevertheless, adherence remains suboptimal even among those who receive free treatment (39.7%), and there is no statistically significant difference compared to those who received subsidized treatment (p=0.082). This observation suggests that factors other than cost alone play a crucial role as major determinants of adherence.

Our study is not without limitations, as our study was retrospective based on recall, which is subject to overestimation. The patients in our study were in different stages and duration of disease which would have affected adherence pattern, and we did not extensively analyze the direct and indirect cost of the treatment.

Conclusion

One-third of patients adhered to medication regimens. Adherence was significantly associated with patient satisfaction, disease awareness and hospital visits while education, socioeconomic status, and disease characteristics showed no association. Free-of-cost treatment did not make a difference in adherence.

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