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Medication Formulation Preference of Mild and Moderate Ulcerative Colitis Patients: a European Survey

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Keywords

Patient preference · Ulcerative colitis · Mesalazine · Oral therapy · Adherence · Compliance

Abstract

Introduction: Patient adherence is a major challenge for the successful management of any chronic disease, and ulcerative colitis (UC) is no exception. Patient adherence is closely related to patient preference of medication and formulation used. **Aim:** The aim of this study was to investigate patient and physician perspectives around UC treatment preference. **Methods:** This study was conducted in France, Germany, Spain, and the UK. Physicians and UK inflammatory bowel disease (IBD) nurses answered an online questionnaire. In addition, adult mild-to-moderate UC patients, treated with oral mesalazine, were invited to answer a 30-min online survey which included a conjoint exercise. **Results:** 400 patients, 160 physicians, and 20 IBD nurses participated in the survey. 68% of patients were taking tablets and 32% granules. Physicians stated that from their perspective patients are more adherent to tablets than granules (76% vs. 24%), patients tended to have better relief of symptoms with tablets (69% vs. 31%), and patients found

tablets to be the most convenient formulation (61% vs. 39%). From the patients' perspective, when questioned which formulation they prefer, 58% answered tablets, 37% granules, and 5% none of these. When patients were asked about some negative attributes of tablets, the highest agreement was for "I would like to take fewer each day" (6.1/10) and "I wish I could take fewer at a time" (5.4/10). **Conclusions:** The majority of UC patients in this survey prefer the tablet formulation. A high strength tablet overcoming the high pill burden could be a good solution to address patient expectations.

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Introduction

Regardless of the disease and its severity, the effectiveness of a prescribed medication is not only dependent on the clinical efficacy of the medication as assessed in clinical trials and long-term data collection, but it also

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hinges on patient adherence. There are various reasons for non-adherence to treatment. These include, among others, forgetfulness, the concern of adverse events and complex dosing regimens. These may negatively influence adherence to medication, both in the clinical trial setting and in real-world practice [1]. Thus, a simple dosing regimen may help patients to improve adherence.

Due to the nature of the disease, ulcerative colitis (UC) patients experience fluctuations between severe disease activity, where induction of remission treatment is required [2], and periods where symptoms are under control and sustained maintenance treatment is often needed [3]. European Crohn's and Colitis Organisation recommends continuing mesalazine treatment in patients with UC even during remission [4]. However, once symptoms are brought under control, maintaining adherence to medication for some UC patients can be challenging.

Non-adherence is associated with many negative consequences. These include increased risk of relapse [5, 6], decreased quality of life [7] and increased risk of colorectal cancer [7].

The dosing regimen has also been shown to have an impact on adherence. A study by Lachaine et al. [8] confirmed that adherence was significantly higher to mesalazine MMX than to any other oral mesalazine tablets, with 40.9% of patients being adherent. Adherence was much lower with the time dependent formulations (26.4%) and the pH dependent formulations (28.5%). These results suggest that a lower pill burden has a positive impact on adherence in UC patients.

The effect of dosing regimen in low, medium, and high adherers has been investigated in a study by Khan et al. [9]. The analysis revealed that there was no significant reduction in the risk of flares when comparing high versus low mesalazine dose among patients with high or medium adherence. However, there was a significant reduction in the risk of flares with high-dose mesalazine among patients with low adherence, thus revealing that a higher dose of oral mesalazine >4 g/day could increase maintenance remission rates in non-adherent patients.

In addition, pharmaceutical formulation prescription according to patient preference may have a positive impact on adherence to treatment and consequently on treatment outcomes. It appears concordant that prescribing the patient-preferred formulation may lead to a better adherence to treatment [10–14]. MacKenzie-Smith et al. [15] reported that patients with UC generally prefer tablets with a lower daily pill burden as well as fewer daily intakes. The development of a higher strength tablet may address both patient preferences.

The aim of this study was to investigate patient and physician preferences for oral UC treatment formulations. The online survey was a replication (with minor modifications) of questions asked previously by MacKenzie-Smith et al. [15].

The survey assessed (i) patients' preference for any oral pharmaceutical forms (e.g., tablets vs. granules), (ii) drivers for patients' preferences, (iii) physicians' perception of patients' preferences, (iv) patients' perceptions of swallowability of different medication forms, and (v) awareness of patients' swallowability problems with oral forms.

Materials and Methods

Study Design

This study was conducted between November 2020 and December 2020 in four European countries (France, Germany, Spain, and the UK). Adult patients, newly diagnosed or with a prior diagnosis of mild (defined as “less than 4 stools/day with/without blood”) to moderate (defined as “4 or more stools per day with/without systemic signs”) [16] UC, were invited to answer a 30-min online survey which included a conjoint exercise. Gastroenterologists, either working in a hospital or office-based setting, as well inflammatory bowel disease (IBD) nurses (UK only) were invited to answer a 30-min online questionnaire.

Questionnaire for Patients

Information was collected on demographics (country and region), time since diagnosis, dosing regimen (number of intakes per day), perceived, and diagnosed disease severity (according to diagnosis by the treating physician), pharmaceutical formulation prescribed, treatment history, previously prescribed treatment, and reasons for treatment change. The 22 questions were either open, yes/no, or multiple choice (see online suppl. material 1; for all online suppl. material, see <https://doi.org/10.1159/000530139>).

Ease of swallowability of pharmaceutical formulations was assessed using pictures and perceived efficacy was assessed by means of a non-validated visual analogue scale (VAS) from 0 to 10. A list of reasons to prefer certain pharmaceutical formulations was assessed by a rating from complete disagreement (0) to complete agreement (10). Medication adherence was defined as the following: adherent; taking up to 80% of medication [5], partly adherent; taking 50–79% of their medication, and non-adherent; taking 50% or less of their medication as prescribed.

Questionnaire for Physicians

The online survey consisted of 14 questions (open, yes/no, or multiple choice) to gather information on: preferred prescribed pharmaceutical formulations for any disease, for UC, by type of patients; perceived patient preference, and reasons underlying the preference; the proportion of patients adherent/partially adherent/non-adherent to treatment, and underlying reasons. Ease of swallowability of pharmaceutical formulations and attributes triggering patient preferences were assessed by means of a non-validated VAS from 0 to 10 (see online suppl. material 2).

Table 1. Patient characteristics

Gender, <i>n</i> (%)	
Male	236 (59)
Age, years	
Mean (range)	41 (18–80)
Time of diagnosis, <i>n</i> (%)	
More than 20 years ago	31 (8)
11–20 years ago	41 (10)
6–10 years ago	78 (20)
3–5 years ago	110 (28)
1–2 years ago	106 (27)
Less than 1 year ago	34 (9)
Currently experiencing a flare, <i>n</i> (%)	
Yes	147 (37)
No	253 (63)
Treatment start, <i>n</i> (%)	
More than 20 years ago	1 (0)
11–20 years ago	25 (6)
6–10 years ago	55 (14)
3–5 years ago	124 (31)
1–2 years ago	145 (36)
Less than 1 year ago	50 (13)
Severity at diagnosis	
Mild	217 (54)
Moderate	183 (46)
Perceived severity (diagnosed mild patients), <i>n</i> (%)	
Mild	124 (57)
Moderate	78 (36)
Severe	15 (7)
Perceived severity (diagnosis moderate patients), <i>n</i> (%)	
Mild	49 (27)
Moderate	53 (29)
Severe	81 (44)
Patients current treatment form, <i>n</i> (%)	
Tablets	272 (68)
Granules	128 (32)

Conjoint Exercise

A conjoint exercise was used to determine the patient and physician preferences. A series of forced-choice questions were asked as a discrete choice exercise, where physicians and patients compared three different treatments at a time. Patients were asked to choose one of three treatments that they would prefer to take, and the physicians were asked to choose a patient profile that they are most likely to treat with each product type. Each patient/physician was provided with 15 different discrete choices. Patients and physicians made a trade-off decision by comparing the attributes of each product (in the case of physicians' product vs. patient); based on the choices, one can assess the importance of each product attribute to the physician or patient choice of a treatment. The data collected from the conjoint analysis was analysed using hierarchical multinomial logit Bayesian estimation and provided the percentage of the patient/physician choice that is decided based on each attribute.

As no treatment (either active or placebo) was administered to the participants in this study, no Ethical Committee approval was sought. All patients, doctors, and IBD nurses consented to participate in this study.

Results

Demographics

Physician Characteristics

Physicians with a primary specialty as gastroenterologist (hospital/office based) in France (*n* = 40; 72%/28%), Germany (*n* = 40; 90%/10%), Spain (*n* = 40; 70%/30%), and the UK (*n* = 40; 100%/0%), and IBD nurses (UK only, *n* = 20) were invited to answer a 30-min online questionnaire. All physicians who were asked to participate, agreed.

Patient Characteristics

Among the 400 individuals (France [*n* = 100], Germany [*n* = 100], Spain [*n* = 100], and the UK [*n* = 100]) with a diagnosis of UC, 217 patients had mild disease activity and 183 had moderate disease. Among patients with mild disease, 57%, 36%, and 7% perceived the severity of their disease as mild, moderate, or severe, respectively. Among individuals with moderate disease activity, the proportion of patients with a perception of the disease severity as mild, moderate, or severe were 27%, 29%, and 44%, respectively (see Table 1). All patients were taking oral mesalazine.

With regard to disease duration, of the 400 patients (236 M, 164 F) who participated in the online survey, the majority of patients had UC for 1–5 years (55%), and a mean age of 41 years. Thirty-seven per cent of patients at the time of the research were experiencing a flare. The majority of patients (67%) started IBD treatment 1–5 years ago. Of these 400 patients, mesalazine formulation was either in tablet form (68%) or granule form (32%).

Formulation Preference

Physician Preference

Physicians were given a series of statements and asked to match the medication formulation (tablets or granules) to each statement. The outcomes are presented in Figure 1.

When physicians were asked which medication formulation would be preferred for “a 5-ASA with a daily dose above 1,500 mg,” 64% and 36% chose to prescribe tablets and granules, respectively. Physicians reported that patients tend to be more adherent to tablets than granules (76% vs. 24%), patients tend to have better relief of symptoms (69% vs. 31%), and patients tend to find tablets the most convenient formulation (61% vs. 39%) (see Fig. 1).

Physician Attributes

With 64% of physicians prescribing tablets, compared to granules (36%), when asked “how much of the treatment

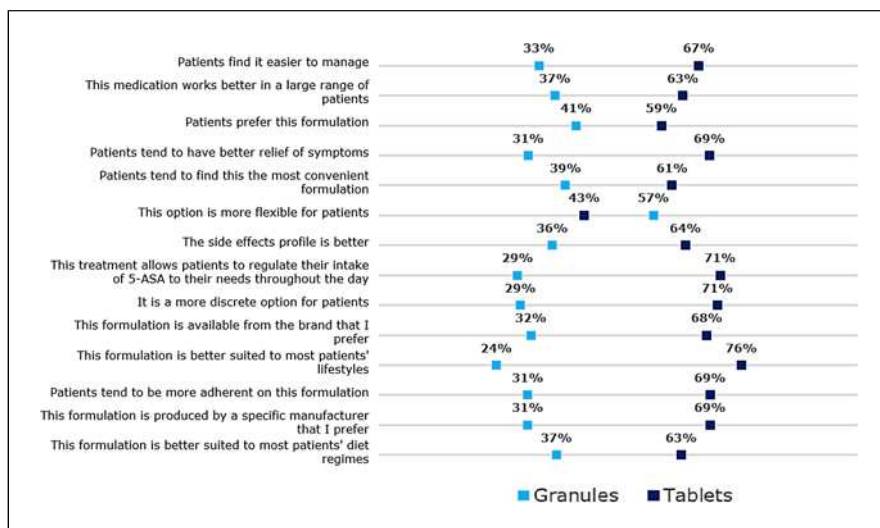


Fig. 1. Physicians' perceptions comparing mesalazine medication formulations.

decision was influenced by your preference and how much was based on the patient's preference?", physicians answered that it is influenced by their recommendation in 58% of cases and in 42%, the decision is influenced by their patients' preference. Physicians' most important attributes for selecting a treatment regimen were as follows: for patients aged 18–35 years, fewer administrations were important when prescribing tablets, whilst for older patients (aged >61 years) tablet size was the most important attribute (Fig. 2).

Overall, independent of age, physicians' most important attributes for selecting a treatment were the frequency of administrations per day (36%), number of tablets per day (34%), and tablet size (31%). These three attributes were weighted equally when selecting a treatment.

Patient Preference

Fifty-eight (58) per cent of patients answered tablets when asked "which formula do you prefer for your UC treatment?", 37% granules and 5% none of these.

On average, as per prescription instructions, patients take their medication in the morning or in the evening (Fig. 3a), and those align with the patients' preference (Fig. 3b). Those who are instructed to take their medication in the middle of the day are more likely not to prefer this. No difference in prescription and patient preference is observed with regard to taking mesalazine with or without meals (Fig. 3).

Positive and Negative Attributes Important to Patients

When patients were asked about positive attributes of tablets, the highest agreement was for "good size, easy to see and handle" (7.6/10), followed by "easy to swallow" (7.5/10), whilst the highest agreement for granules was for "no

problem to take granules in public" (8.4/10) and "pleasant texture" (7.6/10). When patients were asked about negative attributes of tablets, the highest agreement was for "I would like to take fewer each day" (6.1/10) and "I wish I could take fewer at a time" (5.4/10) whilst the highest agreement for granules was "you have to drink a lot of liquid for them to go down" (6.6/10) and "I wish I could take fewer" (5.1/10).

Adherence to Treatment and Perceived Adherence to Treatment

When questioned about treatment adherence, on average, patients claimed to forget to take their medication 1.4 times in the past 2 weeks, with 39% of patients claiming to be fully adherent, 24% forgetting to take their medication once over 2 weeks and 16% forgetting to take their medication twice over 2 weeks (Fig. 4). Physicians tend to think patients are less adherent to treatments compared to patients reported level of adherence. According to physicians, patients are 58.4% adherent, 26.1% partly adherent, and 15.5% non-adherent to their treatment regimen (Fig. 5).

Reasons for Non-Adherence

The main reasons for patients being non-adherent are (i) they forget to take their medication (75%) and (ii) they stop the medication when feeling better (28%) (Fig. 6).

Information Offered to Patients

When physicians were asked "what information is offered to help motivate patients to be compliant with their medication?", differences between granules and tablets were observed in terms of instructions to take the medication with water/mix with food. Physicians tended to recommend to take granules more often with water (36%)

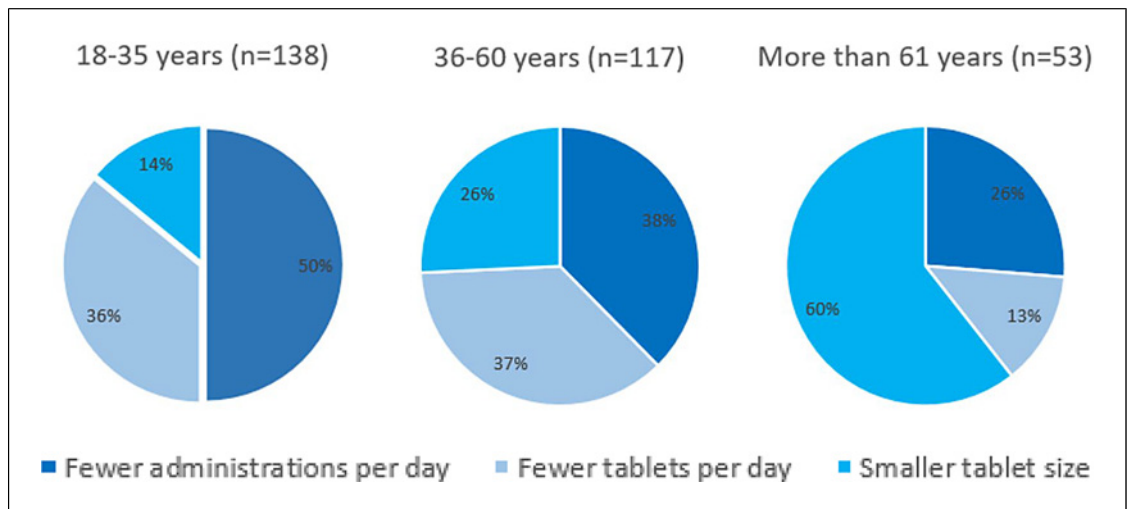


Fig. 2. Patient preference by age.

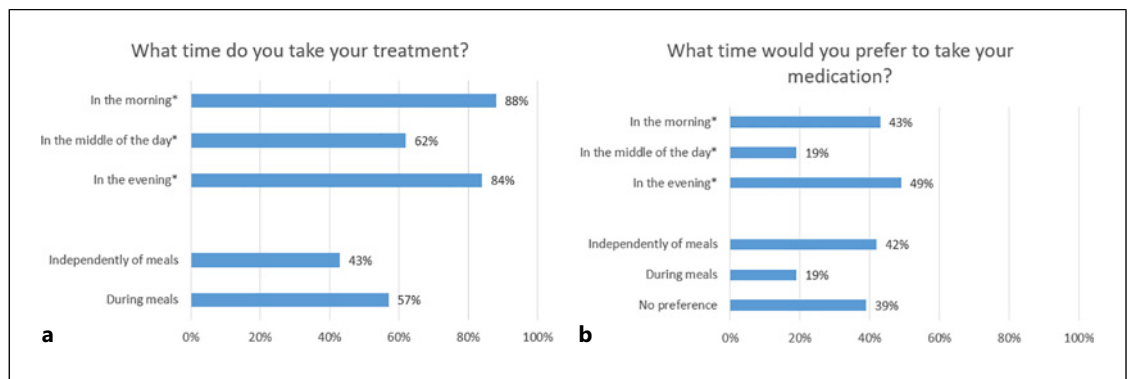


Fig. 3. a, b Timing of treatment and patient preference.

compared to 24% with tablets, and more often with food (17% for granules vs. 8% for tablets). No auto-adaptation of frequency was recommended by physicians.

Switching of Formulations

Patients feel that the main reason for treatment change is that the physician considers another formulation better suited or more effective. Of the patients who switched to granules (from tablets) ($n = 45$), 54.2% reported to still have a relatively positive perception of tablets. Whilst those who had switched to tablets (from granules) ($n = 50$), 46.9% reported to have a strong negative feeling towards granules after the switch. Thirty-seven per cent of patients switched from one formulation to another during their treatment period, in 57% of cases the physician had initiated the treatment change (43% of patients had initiated the change) (see Fig. 7).

Treatment Preference – Physicians

Physicians and patients tend to align on the main reasons for patient preference for granules or tablets. However, they underestimate the impact that simplicity and pill burden has on patients preferring tablets. They also underestimate the impact of pill burden on patients preferring granules (see Table 2).

Swallowability

Ease of swallowability of tablet formulations was assessed in this survey by showing the patients a photo of each available formulation on the market (see online suppl. material 1). Patients were asked about the ease of swallowing tablets using the VAS scale (0 for very difficult to swallow vs. 10 for very easy to swallow). Patients currently taking mesalazine tablets ($n = 271$, 32% of patients chose levels 8–10 [easy to very easy to swallow], 47%, level 5–7 [relatively

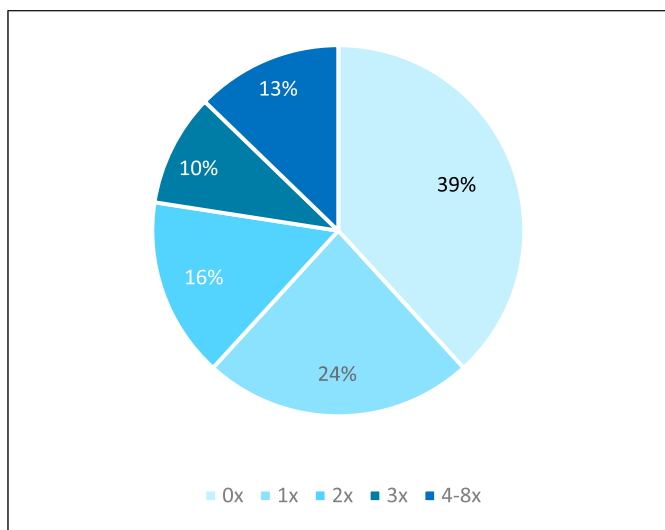


Fig. 4. Number of times medication was forgotten to be taken within a 2 week period.

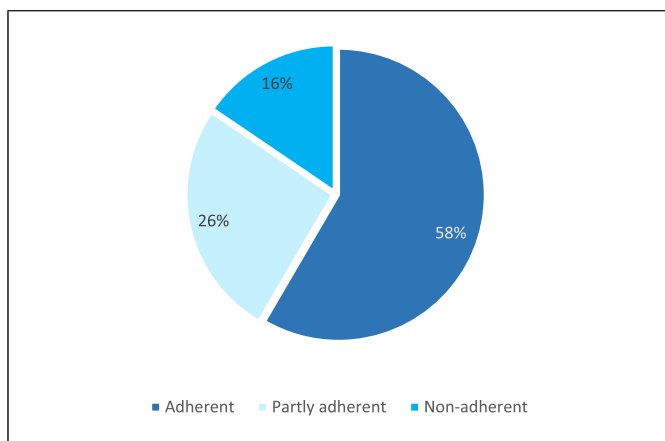


Fig. 5. Perceived patient adherence by physician.

easy to swallow] and 21% chose levels 0–4 [difficult to very difficult to swallow]) to describe the swallowing of the 1,600 mg tablet formulation. Ease of swallowability perception did not differ depending on whether the patients were currently taking mesalazine granules or tablets.

Discussion

The majority of UC patients who participated in the online survey were taking tablet formulations (68%), compared to 32% who were taking granules. These reported percentages were very similar to the physician's

prescription preference. 64% of surveyed physicians reported a preference for tablets, while 36% preferred a granules prescription. With regard to the patient preference for formulations, 58% preferred to take tablets for the treatment of UC, compared to 37% who preferred to take granules.

Reported patient preference for formulation varies in the literature. In one recently reported study by Denesh et al. [17], 298 IBD patients rated acceptability of different forms of medication on 10-point Likert scales and preferences for highest acceptable frequency; significantly more found tablets (91%) to be highly acceptable compared to granules (64%), infusions (33%), and subcutaneous injections (34%; $p < 0.0001$). Tablet preference over granules was also reported by MacKenzie-Smith et al. [15]. Granule preference was reported in the German MUKOSA study, where patients expressed a marked preference for granules (77%) over tablets (13%) [13], and in two other studies, patients with UC reported that the granules have higher acceptability than tablets [18, 19].

Patients included in this research were diagnosed mild-to-moderate, but they often consider that their disease is more severe than what their diagnosis indicates. Reported differences between patient and physician perspectives are common in the literature [20–23].

A recent systematic review to assess IBD patient preferences and perspectives relating to their disease diagnosis, treatment, knowledge needs, and telemedicine was conducted, where 240 citations and 52 studies met the inclusion criteria. Whilst patients' main expectations are symptomatic and pain control, improved quality of life and normal endoscopy, the review concluded that patients with IBD expect more information about their disease progress, shared decision-making, and symptom control [23].

When deciding on a treatment choice, age and number of administrations are important attributes influencing physicians' treatment decisions. Positive attributes of taking tablets include as follows: good size, easy to see and handle, and easy to swallow. The patient treatment preference is driven by the patients' perception and ability to swallow the treatment, and the number of tablets/sachets per administration.

The complexity of patient adherence in UC patients has been investigated in numerous studies. Inconvenient or intrusive medication delivery formulations (e.g., rectal therapies), pill burden and multiple-daily dosing of oral medications have all been associated with poor levels of therapeutic adherence [7]. In this study, 28% of patients stopped taking their medication when feeling better.

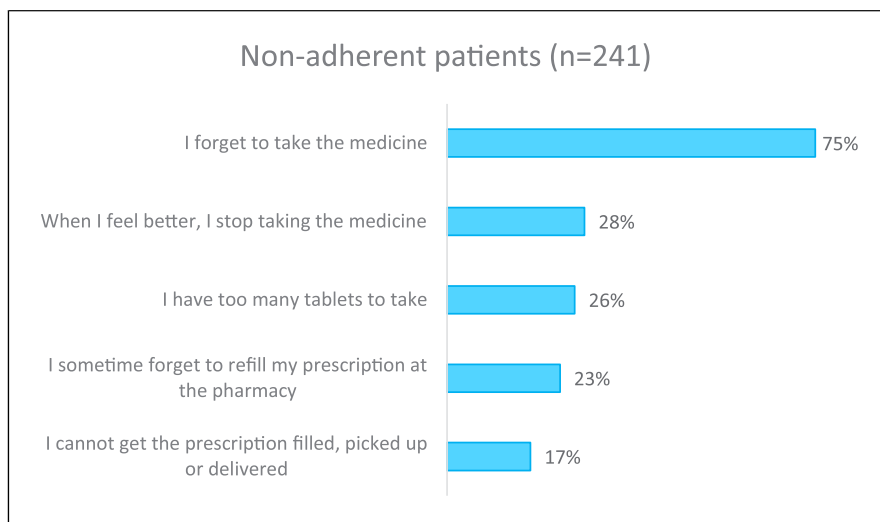


Fig. 6. Reasons for non-adherence.

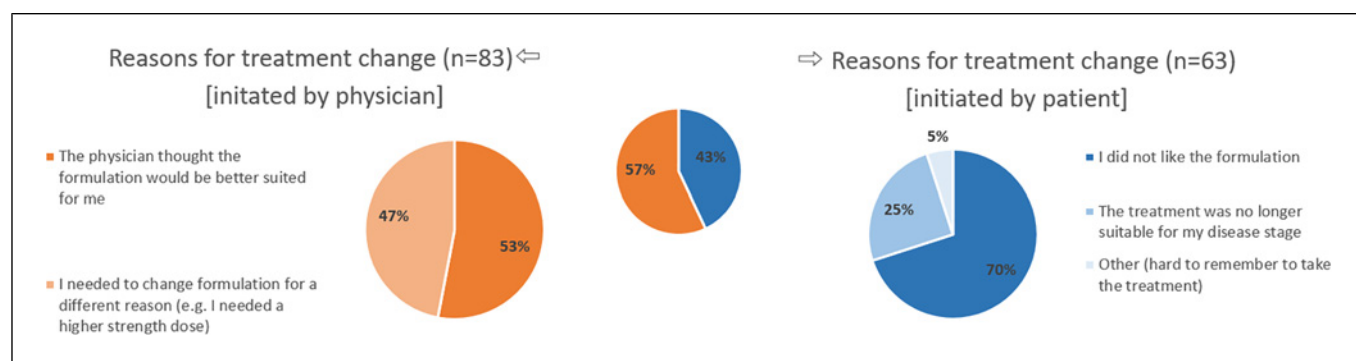


Fig. 7. Reasons for treatment change.

Table 2. Physicians' thoughts on patients' mesalazine preference and patients top reasons for their preference to either tablets or granules

Physicians' thoughts as to why patients prefer tablets (over granules)	Physicians' thoughts as to why patients prefer granules (over tablets)
Tablets are more simple to take [48%]	Granules are more simple to take [31%]
Tablets are more comfortable to take [25%]	Granules are more comfortable to take [45%]
Tablets provide a lower pill burden compared to granules [24%]	Granules provide a lower pill burden compared to tablets [16%]
No preference [3%]	No preference [8%]
Top reasons for patients' preference for tablets include*	Top reasons for patients' preference for granules include*
Ease of use compared to granules [77%]	Ease of use compared to tablets [58%]
Lower number of tablets compared to number of granules [40%]	Ease of swallowing compared to tablets [46%]
Ease of swallowing compared to granules [27%]	Lower number of sachets compared to number of tablets [44%]

*Patients could choose more than one answer.

Reported adherence to medication by patients in this study was generally good, with 58% reporting to take their medication up to 80% of the time, and 26% reporting they took their medication 50–79% of the time. As patients forget to take their medication (46%) and would like to take fewer doses and fewer tablets per dose, a higher strength tablet like the 1,600 mg mesalazine tablet or other high strength mesalazine tablets would be a good solution.

Non-adherence in patients with chronic diseases is high. A systematic review of 17 studies totalling 4,322 adult IBD subjects found non-adherence to oral medications ranging from 7% to 72%, with most studies reporting that 30–45% of patients were non-adherent [24].

Glombiewski et al. [25], a study to investigate medication non-adherence in the general population ($n = 2,512$), found that at least 33% of Germans repeatedly fail to follow their doctor's recommendations regarding pharmacological treatments and only 25% of Germans describe themselves as fully adherent (taking their medication at least 80% of the time), thus highlighting the problem with adherence in patients with chronic diseases.

Multi-method approaches are needed to ensure that the patient adheres to his/her therapeutic regimen. Proposed approaches include the following: firstly, there is a clear desire for patients to be involved in the management of their disease [26]. Elkjaer et al. [27] showed the importance of patient empowerment and the benefits of patients' education compared to a historical control group. Those who received specific education were more likely to take their medication, and length of relapse duration was decreased. Introducing a collaborative approach involving patients in decision-making regarding their medications, so that they have a sense of ownership of their treatment plan is of key importance [28]. Secondly, behavioural interventions [29] such as using the most simplified treatment regimen have demonstrated to be effective – once daily high dose tablets regimens are now the norm for the treatment of UC [30–32], and are recommended in treatment guidelines [16, 33]. Lastly, monitoring medication adherence should be part of patient follow-up visits [28].

This study has several limitations: the explorative study was not powered to detect any statistically significant differences between outcome measures. The absence of bias in the multiple choice questions cannot be guaranteed, despite the effort to provide the responders with the broadest possibilities of realistic choices. Lastly, the visual analogue scale used to assess patient preferences and physician perceptions is non-validated.

In conclusion, the majority of the patients prefer the tablet formulation. A high strength tablet overcoming the pill burden could be a good solution to address patient expectations.

Acknowledgments

The authors would like to thank FMR Global Health for developing and conducting the online survey.

Statement of Ethics

Written informed consent was obtained from the participants to participate in this study.

Conflict of Interest Statement

X.H. has served as a speaker, a consultant, and an advisory board member for Abbvie, Abivax, Alphasigma, Amgen, Arena, Bristol Myers Squibb, Cellgène, Galapagos, Gilead, Eli Lilly, Entero, Ferring, Fresenius-Kabi, Janssen, InDex Pharmaceuticals, Janssen, MSD, Nutricia, Pfizer, Prometheus, Roche, Salix, Sangamo, Takeda, Theravance, Tillotts Pharma, Sanofi-Advantis, Takeda, and Viatrix. S.R.V. has received consulting fees, speakers honorary, and unrestricted research grants from Abbott, Alfasigma, Amgen, Arenapharm, Falk Pharma GmbH, Ferring Pharmaceuticals, Gilead, iQuone, Janssen, MSD, Permamed, Pfizer Inc, Sanofi-Aventis, Takeda, Tillotts Pharma, UCB, and Vifor. J.B. has served as a speaker, a consultant, and an advisory board member for AbbVie, Jansen, MSD, Bristol Meyer Squibb, Tillotts Pharma, Takeda, Pharmacosmos, and Ferring, and has received research funding from Tillotts Pharma, Takeda, Novo Nordisk, MSD, and Bristol Meyer Squibb. H.C.T., R.L., and L.M.S. are employees of Tillotts Pharma, AG.

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Author Contributions

Development of study concept and design: R.L. and L.M.S. Acquisition, analysis, and interpretation of the data and drafting of the manuscript: H.C.T., R.L., and L.M.S. Critical revision of the manuscript for important intellectual content: X.H., S.R.V., and J.B. All authors approved the final version of the manuscript.

Data Availability Statement

Data are available on request due to privacy/ethical restrictions. Further enquiries can be directed to the corresponding author.

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