gastroenterology insights

MDPI

Article

A Practical Approach to Identify Non-Adherence to Mesalamine Therapy in Inflammatory Bowel Disease

Filippo Vernia [1,*], Giorgia Burrelli Scotti [2], Raffaele Borghini [2], Mario Muselli [3], Stefano Necozione [3], Giovanni Moretta [1], Lorenza Scurti [1] and Giuseppe Donato [2]

[1] Division of Gastroenterology, Hepatology, and Nutrition, Department of Life, Health and Environmental Sciences, University of L'Aquila, 67100 L'Aquila, Italy; giovannimoretta95@gmail.com (G.M.); lorenzascurti@gmail.com (L.S.)
[2] Gastroenterology Unit, Department of Translational and Precision Medicine, Sapienza University of Rome, 00185 Rome, Italy; giorgia.burrelliscotti@uniroma1.it (G.B.S.); raffaele.borghini@gmail.com (R.B.); giuseppe.donato@uniroma1.it (G.D.)
[3] Clinical Epidemiology Unit, Department of Life, Health and Environmental Sciences, Public Health Section, University of L'Aquila, 67100 L'Aquila, Italy; mario.muselli@univaq.it (M.M.); stefano.necozione@univaq.it (S.N.)
* Correspondence: filippo.vernia1@gmail.com; Tel.: +39-0862-368760

Abstract: Introduction: Adherence to mesalamine therapy in ulcerative colitis is often inadequate. This affects long-term remission and to some extent the risk of colon cancer. Means for assessing non-adherent behavior are cumbersome, expensive, and/or time consuming. Unless multiple tools are used in association, a proportion of patients with volitional and non-volitional non-adherence is nonetheless undetected. The study was aimed at evaluating to which extent rephrasing a single question on adherence to mesalamine therapy may help identifying patients who are not compliant with medication prescription. **Methods:** One-hundred and seventy-four inflammatory bowel disease outpatients were asked in two consecutive visits, in random order, if they "regularly assumed the prescribed dose of mesalamine" (adherence-centered question—AQ) or "how often they skipped mesalamine pills" (non-adherence centered question—NQ). Answer concordance was evaluated in relation to clinical and demographic variables. **Results:** The concordance between AQ and NQ was low (K = 0.22). Lower compliance to therapy was admitted in 37.4% more patients following NQ than AQ. The reported adherence to AQ was invariably higher than that of NQ, irrespective of the variable taken into consideration. The likelihood of non-concordant answers was non-significantly higher in CD patients than in UC and in patients with shorter disease duration than in those with longstanding disease, but the logistic regression model did not identify individual variables responsible for the different answers. **Conclusions:** Being simple and not requiring additional time expense, centering the question on medication non-adherence identifies a large proportion of patients who would not admit non-adherence or underestimate the number of skipped doses of medication, when directly asked if they are compliant to therapy.

Keywords: adherence; mesalamine; inflammatory bowel disease; ulcerative colitis; Crohn's disease; compliance

Citation: Vernia, F.; Burrelli Scotti, G.; Borghini, R.; Muselli, M.; Necozione, S.; Moretta, G.; Scurti, L.; Donato, G. A Practical Approach to Identify Non-Adherence to Mesalamine Therapy in Inflammatory Bowel Disease. *Gastroenterol. Insights* **2024**, *15*, 754–763. https://doi.org/10.3390/gastroent15030054

Academic Editor: David A. Gerber

Received: 15 May 2024
Revised: 9 August 2024
Accepted: 20 August 2024
Published: 30 August 2024

1. Introduction

Adherence to therapy is defined as the extent to which a person's behavior in terms of taking medications coincides with medical prescription [1]. The behavior has significant impact on the long-term outcome of chronic disease [2,3]; nonetheless, over half of patients affected by chronic illnesses in western countries are not compliant with doctors' recommendations regarding medication prescriptions and dosage [4–6]. The prevalence of non-adherence (NA) is highly dependent on the method used for assessment, which

in turn is influenced by the relative weigh of intentional and non-intentional NA in different diseases [6] and settings. Thus, not surprisingly, the reported prevalence of NA in inflammatory bowel disease (IBD) varies from 7 to 72% in different studies. All considered, the problem involves 30 to 60% of patients [7–11]. This attitude favors relapses and a less favorable disease course in IBD [2,12].

The most reliable tool for assessing NA consists of direct dosage of drug metabolites, but is not widely available and is costly and unsuitable for routine clinical practice. Thus, different tools based on self-report, being costless and accessible, are preferred [13]. However, patients often report good compliance to prescribed medications, knowing that their statement is evaluated by the attending physician, who in turn overestimates the adherence of his patients [14,15]. Volitional NA or covert dose reduction are not adequately assessed by simple self-reporting [6,16] in the absence of time-consuming, specific questionnaires, which again are not routinely used in clinical practice.

Simply rephrasing the questions used for investigating NA has thus been proposed for clinical purposes in a series of IBD patients [17]. It helped to identify a proportion of subjects (24.3%) who did not fully admit NA, when simply asked whether they take their medication as prescribed. The study was carried out in IBD patients undergoing different therapeutic regimens and the current activity of disease was not clearly stated.

Good adherence to therapy is more likely in active disease, but IBD patients in remission are those who most profit from regular maintenance therapy with mesalamine [12,18]. Thus, the present study was aimed at investigating the advantage of rephrasing the question used to assess NA in IBD patients in remission or with minimally active disease. Patients were asked in two consecutive outpatient visits, in random order, if they "regularly assumed the prescribed dose of mesalamine", or "how often they skipped mesalamine pills".

2. Materials and Methods

The study was carried out in patients affected by ulcerative colitis (UC) or Crohn's disease (CD), regularly attending two tertiary IBD referral centers (Gastroenterology, Department of Translational and Precision Medicine, Sapienza University of Rome and Division of Gastroenterology, Hepatology, and Nutrition, Department of Life, Health and Environmental Sciences, University of L'Aquila) treated with mesalamine at a dose of at least 2.4 g/day, irrespective of differing release forms of the drug and pill dosage (500–800–1200 mg). To be considered for enrollment, patients were in remission or mildly active disease, defined as follows. Disease activity was assessed using the Harvey–Bradshaw index (HBI) in CD [19], and the Partial Mayo score in UC [20]. Remission was defined as HBI < 5 for CD and as a partial Mayo score < 1 for UC patients.

During two consecutive visits, patients were interviewed about therapy, using two differently phrased questions, in random order: "Do you regularly assume the prescribed dose of mesalamine?" (adherence-centered question—AQ) or "How often do you skip mesalamine pills?" (non-adherence-centered question—NQ). A random number generator was used to allocate individual patients to the two question sequences (AQ-NQ vs. NQ-AQ).

Overall, a patient was considered adherent when taking >80% of prescribed mesalamine doses. For improving analysis of the patients' behavior, answers were stratified in four adherence scores, as follows. Optimal adherence (>90% prescribed dose, maximum six skipped 800 mg pills or four 1200 mg pills per month) was represented by a score of 4, good adherence (>80% prescribed dose, maximum three skipped 800 mg pills per week) by a score of 3, inadequate adherence (60–80% prescribed dose, between five and nine skipped pills per week) by a score of 2, and poor adherence (<60% prescribed dose, more than ten skipped pills per week) by a score of 1.

Data from patients who experienced relapse or worsening of disease activity in the interval between the two visits were not taken into consideration.

Statistical Analysis

Qualitative variables were expressed as number of cases or percentages, and confidence intervals were calculated. Continuous variables were expressed as mean values and standard deviation (SD) and categorized for further analysis. The Cohen's kappa test was used to measure agreement between adherence-centered and non-adherence-centered questions, and within groups defined by gender, disease type, disease duration, age, and therapy. The Chi square test was used to assess associations between disease type, disease duration, gender, age, and therapy, and non-concordant answers. Logistic regression analysis was used to identify factors influencing the differing answers given to AQ and NQ.

An alpha level of 0.05 was considered statistically significant. The statistical software STATA 18 for Windows was used to perform the analysis.

3. Results

Out of 202 IBD patients in remission or mild activity treated with oral mesalamine eligible for the study, 174 did not show relapse or worsening of the disease between two consecutive outpatient visits. Of these, 110 (63.2%) were affected by ulcerative colitis and 64 (36.8%) by Crohn's disease. A total of 68 (39.1%) were female, and 106 (60.9%) male.

The mean age was 48.89 $\pm$ 17.02 SD. Out of them, 86 were aged less than 45 years, 40 were between 45 and 60 years, and 48 were over 60 years. Disease duration was less than 15 years in 129 patients, and longer in the others.

A total of 144 (82.8%) were on mesalamine monotherapy and 30 (17.2%) on mesalamine in combination with azathioprine or biologic agents.

Patients' characteristics are summarized in Table 1.

Table 1. Patients' characteristics.

NUMBER OF PATIENTS	174 (110 UC; 64 CD)
GENDER	
Male (UC)	106 (66)
Female (UC)	68 (44)
MEAN AGE	48.89 $\pm$ 17.02 SD
AGE GROUPS	
<45 years	86
45–59 years	40
$\geq$60 years	48
UC LOCALIZATION	
E1	15
E2	39
E3	56
CD LOCALIZATION	
L1	11 (6 post-surgery)
L2	22
L3	31 (9 post-surgery)
CD BEHAVIOR	
B1	29
B2	25
B3	10

UC: ulcerative colitis; CD: Crohn's disease; SD: standard deviation.

3.1. Compliance to Therapy

Adherence to mesalamine therapy, evaluated on the basis of one single question, was good. Considering the lowest score as the most reliable, irrespective of whether deriving from the adherence-centered or non-adherence-centered question, 158 (90.8%) patients reported an intake of over 80% of the prescribed dose (score of 3 or 4). Crohn's disease

patients did not differ from those with UC (89.0% vs. 90.1%), as well as males versus females (88.7% vs. 91.2%). The same was true for disease duration (<15 years 89.9% vs. >15 years 88.8%). As far as age is concerned, the intermediate group, aged between 45 and 60 years, was non-significantly less compliant (82.5%) than younger and older patients (91.8% and 91.6%, respectively).

3.2. Concordance between AQ and NQ

Overall, the concordance of answers to the adherence-centered and non-adherence-centered questions was low (Cohen test K value 0.2204). The weighed K value was only slightly higher (0.0298). The reported adherence in AQ was higher than that of NQ in 37.4% of patients. The opposite was rarely observed. The interval of confidence was not overlapping, indicating a significant difference between AQ and NQ (Table 2).

Table 2. Reported compliance to therapy in relation to adherence-centered vs. non-adherence-centered questions.

AQ > NQ	**AQ < NQ**	**AQ = NQ**
65	8	101
37.36% IC 30.15–44.99%	4.6% IC 2.01–8.86%	58.04% IC 50.34–65.47%

Lower adherence to the prescribed mesalamine dose was more likely admitted in response to the non-adherence centered question than the opposite. Intervals of confidence (IC) did not overlap. AQ = adherence-centered question, NQ = non-adherence centered question.

The probability of non-concordant answers was non-significantly higher in CD patients compared to UC (Chi square test, $p = 0.590$) (Table 3) and in patients with disease duration less than 15 years compared to those with longstanding disease (Chi square test, $p = 0.587$) (Table 4).

Table 3. Reported compliance to therapy in relation to diagnosis.

	AQ > NQ	**AQ < NQ**	**AQ = NQ**
UC **110**	38	5	67
	34.55% IC 25.74–44.21%	4.55% IC 1.49–10.29%	60.90% IC 51.14–70.07%
CD **64**	27	3	34
	42.19% IC 29.94–55.18%	4.69% IC 0.98–13.09%	53.12% IC 40.23–65.72%

The likelihood of admitting lower adherence following NQ did not differ in relation to diagnosis. UC = ulcerative colitis, CD = Crohn's disease, AQ = adherence-centered question, NQ = non-adherence-centered question.

Table 4. Reported compliance to therapy in relation to disease duration.

	AQ > NQ	**AQ < NQ**	**AQ = NQ**
DISEASE DURATION **≤15 Years** **129**	51	6	72
	39.53% IC 31.04–48.52%	4.65% IC 1.73–9.85%	55.82% IC 46.81–64.55%
DISEASE DURATION **>15 Years** **45**	14	2	29
	31.11% IC 18.17–46.65%	4.44% IC 0.54–15.15	64.44% IC 48.78–78.13%

Lower compliance to therapy was more frequently reported following NQ, but did not differ in relation to disease duration. AQ = adherence-centered question, NQ = non-adherence-centered question.

Gender did not markedly influence concordance (Chi square test, $p = 0.724$) (Table 5), nor age of patients (Chi square test, $p = 0.992$) (Table 6).

Table 5. Reported compliance to therapy in relation to gender.

	AQ > NQ	**AQ < NQ**	**AQ = NQ**
MALES 106	42	5	59
	39.62% IC 30.25–49.59%	4.72% IC 1.55–10.67%	55.66% IC 45.69–65.31%
FEMALES 68	23	3	42
	33.82% IC 22.79–46.32%	4.41% IC 0.92–12.36%	61.66% IC 49.18–73.29%

Gender did not affect the likelihood of admitting less adherence to therapy following NQ. AQ = adherence-centered question, NQ = non-adherence-centered question.

Table 6. Reported compliance to therapy in relation to age.

	AQ > NQ	**AQ < NQ**	**AQ = NQ**
AGE $\leq$ 45 yrs 86	32	4	50
	37.21% IC 27.02–48.30%	4.65% IC 1.28–11.48%	58.14% IC 47.01–68.70%
AGE 46–60 yrs 40	16	2	22
	40.0% IC 24.87–56.67%	5.0% IC 0.61–16.92%	55.0% IC 38.49–70.74%
AGE > 60 yrs 48	17	2	29
	35.42% IC 22.16–50.54%	4.16% IC 0.51–14.25%	60.42% IC 45.27–74.23%

The likelihood of admitting lower adherence following NQ did not differ in relation to the age group of patients. AQ = adherence-centered question, NQ = non-adherence-centered question.

The concordance between AQ and NQ was better in patients treated with immunosuppressants/biologics plus mesalamine (K = 0.441) than in those on mesalamine (K = 0.168). Nonetheless, the difference between groups did not attain the significance level, likely in relation to the size of the patient series.

The reported adherence to AQ was invariably higher than that of NQ, irrespective of the variable taken into consideration. The intervals of confidence were not overlapping, indicating a significant difference between AQ and NQ within all groups, with the only exception being patients treated with mesalamine plus immunosuppressants/biologics, in which the difference was not significant.

The logistic regression model did not identify individual variables responsible for the different answers given by patients following adherence-centered and non-adherence-centered questions (Table 7).

Table 7. Variables influencing non-concordant answers.

Variable	**OR**	**95% I.C.**		***p*-Value**
Gender				
- **Male**	Ref.			
- **Female**	0.77	0.41	1.45	0.414
Disease				
- **CD**	Ref.			
- **UC**	0.72	0.38	1.35	0.307

Table 7. *Cont.*

Variable	OR	95% I.C.		*p*-Value
Disease duration				
- **<15 yrs**	Ref.			
- **≥15 yrs**	0.73	0.35	1.53	0.406
Age				
- **≤45 yrs**	Ref.			
- **46–60 yrs**	1.1	0.51	2.38	0.806
- **>60 yrs**	0.94	0.44	2.01	0.867
Mesalamine				
- **Monotherapy**	Ref.			
- **Plus IM/biologics**	0.65	0.28	1.5	0.310

Logistic regression model. No variable significantly influenced answer non-concordance. Ref = reference variable. IM = immunomodulators.

4. Discussion

The compliance with the prescribed therapy regimen in patients with chronic disease, IBD included, is lower than that of the general population [4,5,21].

A recent study investigating patients' experience suggested that adherence is impaired by several factors, such as the fear of side effects and a high number of pills [22]; however, non-adherence is often unintentional.

The precise assessment of non-adherence (NA) is difficult, and its prevalence depends upon the tool used, the composition of the study group, and the background population.

Objective methods for assessing adherence in IBD are based on the measurement of the drug or drug metabolite levels in serum and urine [23]. This is the case for 6-thioguanine or 6-methylmercaptopurine in patients on azathioprine/6-mercaptopurine, and the levels of urine salicylates or N-acetyl-5-ASA in those treated with mesalamine [24]. Besides the wide variability observed in spot specimens, the approach is not widely available and is unsuitable for clinical practice.

Indirect "objective" methods, based on pill count, pharmacy refill data, or frequency of medication prescriptions, do not guarantee drug consumption, more so in volitional NA [25]. Thus, a number of different questionnaires based on self-reporting are used for assessing NA. The Medication Adherence Report Scale, using four or five questions (MARS 4–5) [10], the Morisky Medication Adherence Scale (MMAS-8), the Visual Analogue Scales (VAS), and the Forget Medicine scale (FM) have all been validated and are used in IBD [2,26,27]. They provide largely similar results in adherent patients, but correlation is low in less adherent ones [9–11], more so in intentional NA. As pointed out by the authors, these studies compared the results of different tools rather than evaluating the accuracy in quantifying NA.

Thus, at present, individual questionnaires fail to assess some of the factor influencing overall NA, unless multiple, concurrent tools are simultaneously used. This is not feasible in day-to-day clinical practice. The issue is further complicated by the absence of a consistent correlation of NA with clinical and demographic variables, with the possible exception of young age [28].

It can be anticipated that remote monitoring of medication adherence through the use of electronic pill caps and boxes, or smart labels for pill bottles, associated with mobile apps and bidirectional reminder messages, will minimize non-volitional NA [29,30] and help identify those with volitional NA.

But, again, high cost will likely prevent widespread use of this approach.

Engel and co-workers suggested that simply asking patients how often they miss a drug dose helps identify one-fourth of patients who would not admit NA when asked if they were fully adherent to the prescribed therapy [17]. The paper, however, included patients on different therapy regimens and did not specify the clinical activity of disease. Moreover, patients on biologics unexpectedly had a high NA rate. Opposite results were instead reported in other studies, suggesting that patients with active disease and undergoing more aggressive therapies are less prone to NA [31].

Generally speaking, it may be anticipated that adherence is lower in patients with quiescent or mild disease, and this study was focused on this subset of patients, chronically treated with mesalamine.

The prevalence of colon cancer in long-term IBD has been declining over the decades [32,33]. This has been attributed to suppression of or reduction in chronic inflammation, largely depending on long-term use of mesalamine. The real weight of continuous use of mesalamine in reducing the risk of colorectal cancer in the biologic era has been recently debated, and several metanalyses led to partially conflicting data [34,35]. Nonetheless, the active role of mesalamine in chemoprevention has been thoroughly documented in vivo and in vitro [36,37], and suspension of mesalamine at present is not advisable. Since control of inflammation and reduced risk of relapse of active disease require adequate dosage of mesalamine [38], adherence is important. Identification of patients not strictly adherent to recommendations from the attending physician may thus prove rewarding.

The present study was not aimed at investigating the compliance to mesalamine therapy in IBD, but at assessing the advantage of focusing one single question on non-adherence. This proved effective and documented that about one-third of IBD patients in remission or mild activity skip more pills than they would otherwise admit. Overall, 37.4% of patients in our series admitted lower compliance when directly asked how often they skip one mesalamine dose instead of the usual question, asking if they are compliant with the prescribed dose. Females were non-significantly more adherent than males, as well as patients with shorter duration of disease, compared to those diagnosed with IBD more than 15 years before. Concordance between AQ and NQ was slightly better in females than males, but patients with long-lasting disease were more consistent in their answer than those with short duration. These observations are clinically irrelevant. Patients aged over 60 showed a trend toward better adherence, compared to younger age groups. Noteworthy, most data were collected in a tertiary IBD referral center, active for over 50 years. Thus, the prevalence of older cohorts of patients is high compared with other referral centers, and young patients are under-represented. This may have influenced the results and should be taken into consideration when applying conclusions to younger patient series.

Differences in adherence between UC and CD were reported in the past, but results were inconsistent [10,11,39]. Our data did not document a significant difference between the two diseases, although UC patients were non-significantly more concordant in their answers than CD patients (60.9% vs. 53.1%). Patients on combo therapy, biologics, or azathioprine plus mesalamine did not differ from those on mesalamine monotherapy.

The prevalence of NA behavior has been analyzed in depth in a large cohort of Spanish patients affected by chronic illnesses, 322 of them by IBD [6]. Unintentional NA behavior was reported in 21% of patients and intentional NA in 17%. The two conditions coexisted in a further 17% of cases. The figures of unintentional NA are almost identical to those found in our series, using just a single question. The majority of these patients, despite admitting less-than-optimal dosage of mesalamine, still took more than 80% of the prescribed dose. However, one patient in every fifteen, or over 6%, admitted inadequate intake of the drug.

Thus, simple rephrasing identifies two-thirds of patients who do not admit NA, or underestimate the number of skipped doses of medication, when directly asked if they were adherent to the prescribed dose of mesalamine. Limits of the study are related to the subjectivity of the answers in the absence of objective evaluation of NA.

However, the proposed strategy, being simple and not requiring additional time expense, centering the question on medication non-adherence, asking "How often do you skip mesalamine pills?" instead of any form of medication-centered question, such as "Do you regularly assume the prescribed dose of mesalamine?", may provide useful clinical information to the attending physician and help identify those patients who will profit from shortened follow-up visit intervals or proactive strategies aimed at optimizing therapy. As intentional NA coexists with unintentional NA in one-third of these patients, motivational communication, as well as multicomponent interventions (educational, behavioral, cognitive) [40], may further help compliance with medical prescription.

Author Contributions: F.V. and G.B.S.: conceptualization, data curation and original draft preparation; R.B.: data collection and writing—review; G.M. and L.S.: investigation and data collection; M.M. and S.N.: data curation, software and formal analysis of data; G.D.: supervision and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding from any agency, commercial or not-for-profit sectors.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of L'Aquila (protocol code 12/2023; date of approval: 28 March 2023).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Haynes, R.B.; Taylor, D.W.; Sackett, D.L. *Introduction in Compliance in Health Care*; Johns Hopkins University Press: Baltimore, MD, USA, 1979; pp. 1–7.
2. Kane, S.; Huo, D.; Aikens, J.; Hanauer, S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am. J. Med.* **2003**, *114*, 39–43. [CrossRef] [PubMed]
3. Perry, J.; Chen, A.; Kariyawasam, V.; Collins, G.; Choong, C.; The, W.L.; Mitrev, N.; Kohler, F.; Leong, R.W.L. Medication non-adherence in inflammatory bowel diseases is associated with disability. *Intest. Res.* **2018**, *16*, 571–578. [CrossRef] [PubMed]
4. Glombiewski, J.A.; Nestoriuc, Y.; Rief, W.; Glaesmer, H.; Braehler, E. Medication adherence in the general population. *PLoS ONE* **2012**, *7*, e50537. [CrossRef] [PubMed]
5. Nieuwlaat, R.; Wilczynski, N.; Navarro, T.; Hobson, R.; Jeffery, N.; Keepanasseril, A.; Agoritsas, T.; Mistry, N.; Iorio, A.; Jack, S.; et al. Interventions for enhancing medication adherence. *Cochrane Database Syst. Rev.* **2014**, *11*, CD000011. [CrossRef]
6. Cea-Calvo, L.; Marín-Jiménez, I.; de Toro, J.; Fuster-RuizdeApodaca, M.J.; Fernández, G.; Sánchez-Vega, N.; Orozco-Beltrán, D. Different associations of intentional and non-intentional non-adherence behaviors with patient experience with healthcare and patient beliefs in medications: A survey of patients with chronic conditions. *Patient Pref. Adher.* **2020**, *14*, 2439–2450. [CrossRef]
7. D'Inca, R.; Bertomoro, P.; Mazzocco, K.; Vettorato, M.G.; Rumiati, R.; Sturniolo, G.C. Risk factors for non-adherence to medication in inflammatory bowel disease patients. *Aliment. Pharmacol. Ther.* **2008**, *27*, 166–172. [CrossRef]
8. Jackson, C.A.; Clatworthy, J.; Robinson, A.; Horne, R. Factors associated with non-adherence to oral medication for inflammatory bowel disease: A systematic review. *Am. J. Gastroenterol.* **2010**, *105*, 525–539. [CrossRef]
9. Herman, M.L.; Kane, S.V. Treatment nonadherence in inflammatory bowel disease: Identification, scope, and management strategies. *Inflamm. Bowel Dis.* **2015**, *21*, 2979–2984. [CrossRef]
10. Stone, J.K.; Shafer, L.A.; Graff, L.A.; Lix, L.; Witges, K.; Targownik, L.E.; Haviva, C.; Sexton, K.; Bernstein, C.N. Utility of the MARS-5 in assessing medication adherence in IBD. *Inflamm. Bowel Dis.* **2021**, *27*, 317–324. [CrossRef]
11. Severs, M.; Mangen, M.J.; Fidder, H.H.; van der Valk, M.E.; van der Have, M.; van Bodegraven, A.A.; Clemens, C.H.M.; Dijkstra, G.; Jansen, J.M.; de Jong, D.J.; et al. Clinical predictors of future nonadherence in inflammatory bowel disease. *Inflamm. Bowel Dis.* **2017**, *23*, 1568–1576. [CrossRef]
12. Higgins, P.D.; Rubin, D.T.; Kaulback, K.; Kane, S.V. Systematic review: Impact of nonadherence to 5-aminosalicylic acid products on the frequency and cost of ulcerative colitis flares. *Aliment. Pharmacol. Ther.* **2009**, *29*, 247–257. [CrossRef]
13. Hansen, R.A.; Kim, M.M.; Song, L.; Tu, W.; Wu, J.; Murray, M.D. Comparison of methods to assess medication adherence and classify nonadherence. *Ann. Pharmacother.* **2009**, *43*, 413–422. [CrossRef] [PubMed]

14. Soobraty, A.; Boughdady, S.; Selinger, C.P. Current practice and clinicians' perception of medication non-adherence in patients with inflammatory bowel disease: A survey of 98 clinicians. *World J. Gastrointest. Pharmacol. Ther.* **2017**, *8*, 67–73. [CrossRef] [PubMed]
15. Trindade, A.J.; Ehrlich, A.; Kornbluth, A.; Ullman, T.A. Are your patients taking their medicine? Validation of a new adherence scale in patients with inflammatory bowel disease and comparison with physician perception of adherence. *Inflamm. Bowel Dis.* **2011**, *17*, 599–604. [CrossRef] [PubMed]
16. Mountifield, R.; Andrews, J.M.; Mikocka-Walus, A.; Bampton, P. Covert dose reduction is a distinct type of medication non-adherence observed across all care settings in Inflammatory Bowel Disease. *J. Crohn's Colitis* **2014**, *8*, 1723–1729. [CrossRef] [PubMed]
17. Engel, T.; Ungar, B.; Ben-Haim, G.; Levhar, N.; Eliakim, R.; Ben-Horin, S. Re-phrasing the question: A simple tool for evaluation of adherence to therapy in patients with inflammatory bowel disease. *United Eur. Gastroenterol. J.* **2017**, *5*, 880–886. [CrossRef]
18. Lopez, A.; Pouillon, L.; Beaugerie, L.; Danese, S.; Peyrin-Biroulet, L. Colorectal cancer prevention in patients with ulcerative colitis. *Best. Pract. Res. Clin. Gastroenterol.* **2018**, *32–33*, 103–109. [CrossRef] [PubMed]
19. Harvey, R.F.; Bradshaw, J.M. A simple index of Crohn's-disease activity. *Lancet* **1980**, *315*, 514. [CrossRef] [PubMed]
20. Lewis, J.D.; Chuai, S.; Nessel, L.; Lichtenstein, G.R.; Aberra, F.N.; Ellenberg, J.H. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm. Bowel Dis.* **2008**, *14*, 1660–1666. [CrossRef]
21. Hope, H.F.; Hyrich, K.L.; Anderson, J.; Bluett, J.; Sergeant, J.C.; Barton, A.; Cordingley, L.; Verstappen, S.M.M.; RAMS Co-Investigators. The predictors of and reasons for non-adherence in an observational cohort of patients with rheumatoid arthritis commencing methotrexate. *Rheumatology* **2020**, *59*, 213–223. [CrossRef]
22. Amiesimaka, O.I.; Aluzaite, K.; Braund, R.; Schultz, M. "It's just like putting your socks on": Patients' perspectives on inflammatory bowel disease medication adherence. *Explor. Res. Clin. Soc. Pharm.* **2023**, *12*, 100385. [CrossRef] [PubMed]
23. Gilissen, L.P.; Wong, D.R.; Engels, L.G.; Bierau, J.; Bakker, J.A.; Paulussen, A.D.C.; Romberg-Camps, M.J.; Stronkhorst, A.; Bus, P.; Bos, L.P.; et al. Therapeutic drug monitoring of thiopurine metabolites in adult thiopurine tolerant IBD patients on maintenance therapy. *J. Crohn's Colitis* **2012**, *6*, 698–707. [CrossRef]
24. Gifford, A.E.; Berg, A.H.; Lahiff, C.; Cheifetz, A.S.; Horowitz, G.; Moss, A.C. A random urine test can identify patients at risk of mesalamine non-adherence: A prospective study. *Am. J. Gastroenterol.* **2013**, *108*, 249–255. [CrossRef]
25. Steiner, J.F.; Koepsell, T.D.; Fihn, S.D.; Inui, T.S. A general method of compliance assessment using centralized pharmacy records. Description and validation. *Med. Care* **1988**, *26*, 814–823. [CrossRef] [PubMed]
26. Ediger, J.P.; Walker, J.R.; Graff, L.; Lix, L.; Clara, I.; Rawsthorne, P.; Rogala, L.; Miller, N.; McPhail, C.; Deering, K.; et al. Predictors of medication adherence in inflammatory bowel disease. *Am. J. Gastroenterol.* **2007**, *102*, 1417–1426. [CrossRef]
27. SOLE Study Group. Translation and initial validation of the Medication Adherence Report Scale (MARS) in Italian patients with Crohn's Disease. *Dig. Liver Dis.* **2019**, *51*, 640–647. [CrossRef] [PubMed]
28. Spekhorst, L.M.; Hummel, T.Z.; Benninga, M.A.; van Rheenen, P.F.; Kindermann, A. Adherence to oral maintenance treatment in adolescents with inflammatory bowel disease. *J. Pediatr. Gastroenterol. Nutr.* **2016**, *62*, 264–270. [CrossRef]
29. Axelrad, J.; Long, M.; Horst, S.; Afzali, A.; Sapir, T.; Fajardo, K.; De Felice, K.; Sandler, R.; Cross, R. A novel remote patient and medication monitoring solution to improve adherence and persistence with Inflammatory Bowel disease therapy (ASSIST Study): Protocol for a randomized controlled trial. *JMIR Res. Protoc.* **2022**, *11*, e40382. [CrossRef]
30. Miloh, T.; Shub, M.; Montes, R.; Ingebo, K.; Silber, G.; Pasternak, B. Text messaging effect on adherence in children with inflammatory bowel disease. *J. Pediatr. Gastroenterol. Nutr.* **2017**, *64*, 939–942. [CrossRef]
31. Selinger, C.P.; Eaden, J.; Jones, D.B.; Katelaris, P.; Chapman, G.; McDonald, C.; Smith, P.; Lal, S.; Leong, R.W.; McLaughlin, J.; et al. Modifiable factors associated with nonadherence to maintenance medication for inflammatory bowel disease. *Inflamm. Bowel Dis.* **2013**, *19*, 2199–2206. [CrossRef]
32. Munkholm, P. Review article: The incidence and prevalence of colorectal cancer in inflammatory bowel disease. *Aliment. Pharmacol. Ther.* **2003**, *18*, 1–5. [CrossRef] [PubMed]
33. Burisch, J.; Lophaven, S.; Munkholm, P.; Langholz, E. Surgery, cancer and mortality among patients with ulcerative colitis diagnosed 1962–1987 and followed until 2017 in a Danish population-based inception cohort. *Aliment. Pharmacol. Ther.* **2022**, *55*, 339–349. [CrossRef]
34. Carrat, F.; Seksik, P.; Colombel, J.F.; Peyrin-Biroulet, L.; Beaugerie, L.; CESAME Study Group. The effects of aminosalicylates or thiopurines on the risk of colorectal cancer in inflammatory bowel disease. *Aliment. Pharmacol. Ther.* **2017**, *45*, 533–541. [CrossRef] [PubMed]
35. Qiu, X.; Ma, J.; Wang, K.; Zhang, H. Chemopreventive effects of 5-aminosalicylic acid on inflammatory bowel disease-associated colorectal cancer and dysplasia: A systematic review with meta-analysis. *Oncotarget* **2017**, *8*, 1031–1045. [CrossRef] [PubMed]
36. Słoka, J.; Madej, M.; Strzalka-Mrozik, B. Molecular mechanisms of the antitumor effects of mesalazine and its preventive potential in colorectal cancer. *Molecules* **2023**, *28*, 5081. [CrossRef]
37. Hsiao, S.W.; Yen, H.H.; Chen, Y.Y. Chemoprevention of colitis-associated dysplasia or cancer in inflammatory bowel disease. *Gut Liver* **2022**, *16*, 840–848. [CrossRef]
38. Feagan, B.G.; Macdonald, J.K. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst. Rev.* **2012**, *10*, CD000544. [PubMed]

39. Eindor-Abarbanel, A.; Naftali, T.; Ruhimovich, N.; Bar-Gil Shitrit, A.; Sklerovsky-Benjaminov, F.; Konikoff, F.; Matalon, S.; Shirin, H.; Milgrom, Y.; Broide, E. Revealing the puzzle of nonadherence in IBD—Assembling the pieces. *Inflamm. Bowel Dis.* **2018**, *24*, 1352–1360. [CrossRef]
40. Gohil, S.; Majd, Z.; Sheneman, J.C.; Abughosh, S.M. Interventions to improve medication adherence in inflammatory bowel disease: A systematic review. *Patient Educ. Couns.* **2022**, *105*, 1731–1742. [CrossRef]