EDITORIAL

Prevalence, predictors, and clinical consequences of medical adherence in IBD: How to improve it?

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Abstract

Inflammatory bowel diseases (IBD) are chronic diseases with a relapsing-remitting disease course necessitating lifelong treatment. However, non-adherence has been reported in over 40% of patients, especially those in remission taking maintenance therapies for IBD. The economical impact of non-adherence to medical therapy including absenteeism, hospitalization risk, and the health care costs in chronic conditions, is enormous. The causes of medication non-adherence are complex, where the patient-doctor relationship, treatment regimen, and other disease-related factors play key roles. Moreover, subjective assessment might underestimate adherence. Poor adherence may result in more frequent relapses, a disabling disease course, in ulcerative colitis, and an increased risk for colorectal cancer. Improving medication adherence in patients is an important challenge for physicians. Understanding the different patient types, the reasons given by patients for non-adherence, simpler and more convenient dosage regimens, dynamic communication within the health care team, a self-management package incorporating enhanced patient education and physician-patient interaction, and identifying the predictors of non-adherence will help devise suitable plans to optimize patient adherence. This editorial summarizes the available literature on frequency, predictors, clinical consequences, and strategies for improving medical adherence in patients with IBD.

INTRODUCTION

Inflammatory bowel disease (IBD) is a multifactorial entity with both genetic and environmental factors contributing to disease pathogenesis[1]. Worldwide, the incidence rates for IBD vary from 0.5 to 24.5 per 100 000 person-years[2], with the majority of patients being disabled during various parts of their lives. This characteristic may also suggest poor adherence (i.e. a percentage of the prescribed doses is not taken) outside the clinical trial settings[3-5].

Treatment of IBD can involve several medications with varying regimens, dietary modifications, and potentially, surgery, depending on symptoms, severity of illness, and response to treatment. Adherence to the pharmacological treatment is a complex process, where the doctor-patient relationship, treatment regimen and other disease-related factors play key roles. The undesirable side effects of some medications (e.g. weight gain, cushingoid appearance, and immune suppression) and the complex treatment regimens for IBD patients (e.g. varying dosing schedules and pill quantities for each medication) are likely to disrupt adherence and the effective management of this condition. These data are consistent with the hypothesis that many patients engage in an implicit cost-benefit analysis in which beliefs about the necessity of their medication are weighed against concerns about the potential adverse effects of taking it, and that these beliefs are related to medication adherence, as in other chronic conditions[6]. This scenario has been also proven in patients with IBD in a very recent paper[7]. In contrast, the impact of medication non-adherence on the hospitalization risk and health care costs in chronic conditions (e.g. diabetes, hypertension, and congestive hearth failure) is enormous[8]. It has been estimated to cost as much as $100 billion in the US annually, and accounts for 10% of all hospital admissions.

However, there are no studies that directly assess the costs associated with non-adherence in patients with IBD. Recently, it has been estimated in the UK that relapse was associated with a two- to threefold increase in the costs for those who did not require hospital care and a 20-fold increase for those who were hospitalized[9].

Research on adherence in IBD is limited. Studies in adults have revealed medication non-adherence rates ranging from 35% to 45%[3,5,10]. Unfortunately, most of these studies used different, unimodal indirect assessment methods including non-standardized self-report questionnaires, non-standardized patient/parent interviews, pill counts, pharmacy records, and measurements of health outcomes. A drawback of this method is that it can overestimate adherence, and its accuracy depends on the patient's cognitive abilities, the honesty of replies, as well as the interviewer's correct interpretation of responses. The patient may forget doses taken or missed. Prescription refills are also considered questionable for assessing dosing compliance because they provide no information on timing or quantity of pills ingested. In addition, pill counts are often erroneous because patients do not always return bottles with leftover pills. Thus, until now, the methods for assessing compliance have varied in terms of prospective *versus* retrospective or objective *versus* subjective measurement, target behaviour assessed (e.g. consumption of medication and refill of prescription), medication assessed, and method of assessment. This variability resulted in different estimates of the prevalence of non-adherence and diminished generalizability and the validity of data. Furthermore, these studies were limited by potential response bias in the self-report measures or behavioural manipulation, such as discarding pills to influence pill count data[11].

In general, direct methods for measuring medication adherence include drug concentration monitoring through blood and urine assays. This strategy is expensive and inconvenient for patients, and, moreover, only a limited number of drugs can be monitored in this manner. The bioavailability and completeness of absorption of various drugs, as well as the rate of metabolism and excretion, are factors that make it difficult to correlate drug concentrations in blood or urine with adherence. The ability of direct methods to identify non-adherence also depends on the accuracy of the test and the degree to which the patient was non-adherent before the urine or blood sample was taken. Drug concentration monitoring can also be misleading because most drugs are rapidly absorbed following administration. Thus, even if numerous doses were omitted, yet a few doses were taken immediately prior to the blood test, the results would show the presence of a moderate amount of drug, or *vice versa*.

In IBD, bioassays measuring 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine nucleotide (6-MMPN) levels have been suggested as potentially useful objective adherence markers for 6-mercaptopurine (6-MP)/azathioprine (AZA)[11,12]. However, they have not been validated against traditional measures of adherence. Moreover, like other bioassays, they are subject to pharmacokinetic variation in absorption, metabolism,

and excretion. Despite their limitations, bioassays provide key adherence data in that they can confirm ingestion. Non-therapeutic metabolite levels can suggest either non-adherence or pharmacokinetic influence, or both; cases where both 6-TGN and 6-MMPN levels are subtherapeutic/unquantifiable are likely to indicate non-adherence. Thus, although there is no gold standard in adherence assessment, and limitations exist with any measure of adherence, both behavioural and biological measures offer unique data that could be used to better understand non-adherence. Moreover, determining the most advantageous approach to assessing adherence is critical to the clinical care of these patients. This editorial summarizes the available literature on frequency, predictors, clinical consequences, and strategies for improving medical adherence in patients with IBD.

PREVALENCE OF NON-ADHERENCE IN IBD

In normal clinical practice, adult studies have revealed medication non-adherence prevalence rates ranging from 35% to 72%[3,5,10,13,14]. For example a cross-sectional study of US outpatients with quiescent ulcerative colitis (UC) found that only 40% were adherent to maintenance mesalazine (mesalamine) therapy[3]. In the UK, approximately 15% of patients fail to even redeem prescriptions at the pharmacy[15]. Moreover, treatment non-adherence rates might vary considerably between countries. In Europe, a survey of 203 IBD patients revealed self-reported non-adherence rates ranging from 13% in France, to 26% in Italy, 33% in the UK and 46% in Germany. The overall non-adherence rate was 29% across Europe[4], where non-adherence was defined as taking < 80% of prescribed medication. Similarly high rates of non-adherence were reported from Eastern Europe. Overall intentional non-adherence was reported by 38.9% of patients, and 18.6% of the patients at least once discontinued the treatment[5]. In a Canadian study, UC diagnosis was associated with higher risk of non-adherence (OR: 4.42)[16].

Significant differences may exist in children and adolescents, given the complex developmental challenges unique to childhood and adolescence, including the maturation of cognitive and behavioral patterns (e.g. health beliefs) that affect self-management. However, only a few studies have examined adherence rates in pediatric IBD, with the results indicating the prevalence of non-adherence ranging from 50% to 66%[17,18]. Moreover, special attention should be paid to the method of assessment, because significant differences may be present in objective methods *versus* subjective self-report methods. In a recent paper, Hommel *et al*[11] reported an objective non-adherence frequency of 38% for 6-MP/AZA and 49% for 5-ASA medications, while the subjective non-adherence frequency was reported to be as low as 6% for 6-MP/AZA and 3% for 5-ASA. In contrast, in a prospective, single-center study from Germany[19] both objective (9.2%) and self-reported (7.1%) non-adherence rates were low in 65 adult Crohn's disease (CD) patients.

PREDICTIVE FACTORS FOR NON ADHERENCE AND CLINICAL CONSEQUENCES

Gender

Conflicting data are available on the role of gender in predicting non-adherence to medical therapy. Kane *et al*[3] and Mantzaris *et al*[20] related poor adherence with the male gender. In the study by Kane *et al*[3] non-adherent patients were statistically more likely to be males (67% *vs* 52% in adherent patients). Gender interactions also proved relevant in a recent population-based study, in which young females proved to be less adherent than males[17], while other studies could not find a significant difference[5]. In addition there may be different factors affecting medication adherence in men and women. In the study by Ediger *et al*[16] a diagnosis of ulcerative colitis (*vs* Crohn's disease) having high scores on the Obstacles to Medication Use Scale and a low level of the personality trait of agreeableness, were important predictors of low adherence in males. For women, important predictors of low adherence included an age younger than 30 years, having high scores on the Obstacles to Medication Use Scale, and having a low level of the personality trait of agreeableness. Immunosuppressant use was associated with high adherence in women.

Similarly, data are conflicting with regards to marital status, type of education, employment status, or type of disease. A higher education level and full time employment was also associated with a non-adherent patient behavior in some[5,16,21], but not all, studies[14].

Age and disease duration

Age seems to be an important factor, as younger patients tend to be less adherent than older patients[10,18]. In a recent Italian study[22] non-adherence was 43% in patients < 40 years old compared to 34% in those older than 40 years (*P* = 0.041, OR: 1.5, CI: 1.01-2.13). Recently, diagnosis and disease duration shorter than 5 years was also associated with significantly worse adherence (24% of the patients) than a longer-standing disease (15% of the patients; *P* = 0.001, OR: 2.1, CI: 1.30-3.39) in the same study. Moreover, non-adherence increased to 75% when both age (< 40 years) and disease duration (< 5 years) were considered. This may have to do with the fact that IBD primarily affects young individuals with greater personal and social goals, being busy at work, and having some degree of rebelliousness, but it may also be that a younger age is associated with a more recent diagnosis, with less experience with the burden of relapse or surgery. This was, however, not a universal finding[5].

Phenotype, disease activity and surgery

In UC, Kane *et al*[3] reported by means of univariate analysis, that male gender, being without a relationship partner, left-sided disease, and a history of more than four concomitant medications, were negatively associated with adherence. Conversely, being married, having a recent colonoscopy, and a greater extent of disease supported

adherence. A UK-based cross-sectional study, using data extracted from general practitioner (GP) clinical records, examined the usage of long-term aminosalicylate therapy in patients with UC[13]. It was found that 38% of the patients with extensive colitis, 37% of the patients with left-sided colitis and 46% of those with proctitis did not take medications for maintenance therapy. This was not, however, confirmed in all studies[5].

An association between medical adherence and complicated disease course in CD was reported by Spanish authors[14]. Better adherence was significantly associated with a more complicated disease course (steroid dependency, steroid refractoriness, need for infliximab treatment, hospitalization, or surgery) in patients with short disease duration. Similarly, in a recent Hungarian study[23], a higher number of previous surgeries was associated with improved self-reported adherence in patients with CD.

Active disease was associated with higher adherence, even if steroids were included in the treatment regimen in both CD and UC[10]. In contrast, other studies reported low adherence rates after long-term remission[3,22]. Very high non-adherence rates (74.3%) were reported for azathioprine in CD patients who were in long-term (> 48 mo) clinical remission[20].

Moreover, a direct association between adherence and risk of relapse was reported in UC. Kane *et al*[24] prospectively studied the risk factors associated with relapse among 99 patients who were in remission for more than six months and prescribed 5-ASA maintenance therapy. The clinical recurrence of UC was defined as four or more bowel movements per day. At a 12-mo follow-up, 19 of 86 patients had recurrent disease, 13 (68%) of whom were non-adherent. Patients who were non-adherent with medication had a greater risk of recurrence than adherent patients (OR: 5.5, 95% CI: 2.3-13). A Kaplan-Meier curve constructed to compare outcomes stratified by adherence status for 24 mo also showed that UC patients adherent to their 5-ASA therapy had a significantly greater chance of remaining in remission than those who were non-adherent (89% *vs* 39%; *P* = 0.001).

Drug type and dosing regimes

Non-adherence to therapy might also be due to the drug formulation causing discomfort (difficulty in swallowing tablets or using enemas) or side effects (pain, abdominal distension, or difficulty in retaining enemas). Most studies are consistent in finding that topical therapy with enemas, suppositories or foams is more likely to be associated with non-adherence than oral therapy. In an Italian study[22], topical therapy with enemas was associated with significantly more non-adherence (68% of users) than oral therapy (40% of users; *P* = 0.001, OR: 0.25, CI: 0.11-0.60). Similarly, analyzing a national prescription-based database also showed that overall adherence to mesalazine was unexpectedly low and the rectal formulation was among the factors influencing non-adherence[25]. Enemas were judged difficult to use, painful or to cause bloating, and were difficult to manage during working hours.

The association between the type of oral medications and non-adherence is more controversial. The undesirable

side effects of some medications (e.g. weight gain, cushingoid appearance, or immune suppression) and the complex treatment regimens for IBD patients (e.g. varying dosing schedules and pill quantities for each medication) are likely to disrupt adherence and effective management of this condition. Interestingly, some studies did not report a direct association. For example, in the study by Cervený et al[5], the non-adherence rate at any time point was 40% on aminosalicylates, 29% in patients on systemic steroids, and 31% in patients on immunosuppressants in CD. Similar data were reported in UC, supporting the notion that adherence is influenced by multiple parallel factors, including gender, age, disease activity, and so on. Interestingly, the same study, using a factor analysis, reported a strong influence of adverse drug effects on adherence. Intentional non-adherent behavior due to adverse drug effects was the second most common cause reported during a patient interview. In addition, adverse drug effects were independently proven by factor analysis to affect a patient's confidence in treatment.

Reasons for non-adherence to oral therapy include multiple daily doses and a high number of concomitant medications. In the study by Kane et al[3], besides being males, single, and having left-sided disease, non-adherent patients were statistically more likely to be taking four or more concomitant medications (60% vs 40%). Similarly, in the study of Shale and Riley[21], in addition to being young, having education beyond the age of 16 years and being in full-time employment, being prescribed a 3-times-a-day regimen was identified as predictor for non-adherence. The need to take medicine during working hours ($P = 0.001$, OR: 3.5, 95% CI: 2.27-5.26), and multiple daily doses ($P = 0.045$, OR: 2.8, 95% CI: 0.99-7.70) were significantly associated with non-adherence in adults[22], which was also confirmed by other studies[20,21]. Similarly, adolescents whose regimen involved more than one daily medication administration had more adherence barriers[26]. In addition, lack of time and medication side effects were also commonly reported barriers. Other adolescent-reported barriers included missing medication due to feeling well or discontinuing medication based on the belief that the medication was not working. In contrast, a recent retrospective cohort study suggests that adherence in UC patients is independent of drug formulation[27]. Magowan et al[27] used records from multiple US health plans to compare the refill prescription profiles of 1680 UC patients who had initiated 5-ASA therapy with one of four formulations: delayed-release mesalamine (Asacol), controlled-release mesalamine (Pentasa), sulfasalazine (Azulfidine), or balsalazide (Colazal). Upon initiation of treatment, the median daily dose and respective tablet/capsule load were 2.4 g (6 tablets) for delayed-release mesalamine, 4.0 g (16 capsules) for controlled-release mesalamine, 2.0 g (4 tablets) for sulfasalazine, and 6.75 g (9 capsules) for balsalazide. Comparison of the refill profiles over 12 mo, however, indicated that adherence in these patients was not affected by formulation type and/or dose regimen.

The use of once-daily treatment for improving medical compliance is further supported by a recent randomized, multicentre, investigator-blinded study of 362 patients who were randomised to receive mesalazine granules (Pentasa®) 2 g once daily or 1 g twice daily. It showed an 11.9% greater remission rate at one year (73.8% vs 63.6%, respectively) in the single daily dose group[28]. Patient questionnaires showed significantly greater self-reported compliance ($P < 0.05$) and acceptability ($P < 0.001$) in the once-daily group. High compliance rates were reported for the once-daily MMX mesalazine and Salofalk® granules[29,30]; therefore the effect is likely to be generic rather than compound-specific. Thus, new mesalazine formulations offer a simplified dose regime, resulting in presumably improved long-term compliance that can be considered an important advantage in the management of UC patients.

Patient-doctor relationship

The partnership between patient and the treating physician is of utmost importance in determining medical adherence, where effective patient-physician dialog is central to promoting patient adherence[22]. Studies have also shown that the interaction between the patient and the physician has a huge impact on health outcomes and costs. Both the quality and quantity of the visits are important. Sewitch et al[10] found an increased risk of intentional non-adherence to be associated with being treated by the same physician for more than one year, not scheduling another appointment, and greater total discordance between the patient and the physician. Similarly, a higher degree of intentional non-adherence in the study by López San Román et al[31] was associated with greater patient depression and patient-physician discord. Patients trusted their physician less, and considered themselves to be less informed about their treatment.

A direct association between the total number of health care visits and medical adherence was proven in children with CD[18]. In addition, patients under specialist care were significantly more likely to be taking an aminosalicylate than those definitely discharged to general practitioner's care in adults with UC[13]. In contrast, however, a European cohort showed no correlation between the number of times an IBD patient had seen the physician and self-reported medication adherence rates[4].

STRATEGIES TO IMPROVE ADHERENCE

A large body of evidence supports the key role of the physician-patient relationship in achieving higher patient medication-adherence rates. Psychology literature points out to using COPE principles as a way for physicians to improve their relationship with patients and optimize patient adherence to their medication. The COPE principles encompass the following: communicate with patients; obtain patient's commitment to therapeutic objectives; promote emotional/psychological/physical support as necessary; educate the patient and their family. In addition, trust in the physician and continuity of care by the same doctor are also important to patients.

In the everyday practice, the physician's willingness to allow patients to contribute input and become involved in their illness during the medical visits was suggested to

facilitate treatment decisions that are meaningful to both parties[32]. The consultation style adopted by the physician is also an important factor in building the physician-patient relationship. Indeed, when physicians adopted a mutual, co-operative relationship, and exhibited less control dominance, a reported increase in patient adherence and satisfaction was observed.

During consultations, all factors affecting adherence need to be explored, including the patient's level of knowledge, belief systems and support environment, for example their network of family and friends.

Written and oral education (on the disease, management algorithm and medications) has been shown to increase adherence by approximately 6%-25%[33]. Written information is more effective when verbally reinforced. In addition, a study of 69 patients with IBD demonstrated improved knowledge, patient satisfaction, and a positive trend towards greater adherence in patients who had undertaken the IBD education program (consisting of pamphlets and ad hoc physician education), which is the standard of care in many referral centers, compared with patients who received standard care[34].

Guided self-management involving the provision of a shared set of guidelines containing action plans for the prevention of disease activity and/or symptom relief, have been used in the management of many chronic illnesses. A randomized, controlled study evaluating guided self-management programs in patients with IBD has demonstrated, a reduction in hospital visits without an increase in morbidity and greater confidence in the patient's ability to cope with IBD[35]. Further studies are needed in order to assess whether such interventions will improve adherence to medication and clinical outcomes in patients with IBD. Furthermore, a special form of patient education could be successfully implemented using an internet-based patient education platform, as suggested by Elkjaer et al[36].

Another approach that could be used to optimize patient adherence involves individualized therapy, where physicians review the patient's disease and therapeutic history, and identify which treatment(s) were effective/ineffective in the past to avoid prescribing the same unsuccessful medication. Simplification of treatment (e.g. reduced dosing frequency and the use of long-acting agents) and avoidance of unnecessary multiple concomitant medications is preferable, where feasible, and are associated with better adherence and improved clinical outcome[3,21,24]. Furthermore, this patient review process could also provide predictive information on medication non-adherence behavior, and thus help identify those patients at high risk who might require longer consultation slots than those at low risk. Patients could also be prompted to take their medications via simple pill-taking cues, such as placing pills close to something they use daily, for example the toothpaste, breakfast table, glasses/contact lenses case, and so on. In addition, telephone support, postal reminders, and setting alarms on watches/mobile phones have been suggested. Nevertheless, combining education and behavioral interventions has been suggested to be the most effective approach to improving adherence.

CONCLUSION

Non-adherence is common in IBD and has been reported in 40%-60% of patients, especially those in remission and taking maintenance therapies for IBD. The economical impact of medication non-adherence, including absenteeism, hospitalization risk, and health care costs in chronic conditions, is enormous. The causes of medication non-adherence are multi-factorial, including forgetfulness, gender, new diagnosis, disease phenotype, patient-physician relationship, complicated dosing regimens, side-effect profile of the drugs, and treatment delivery methods. The associated factors may vary in each country because of the difference in the healthcare systems and the population. Moreover, a gold standard method to estimate the prevalence of non-adherence does not exist. Subjective assessment may underestimate adherence, while recent episodes of non-adherence may result in high non-adherence rates if measured by direct methods (e.g. drug concentration monitoring using blood and urine assays). Moreover, this latter strategy is expensive and inconvenient for patients, and only a limited number of drugs can be monitored in this way. Poor adherence may result in more frequent relapses, disabling disease course, and in ulcerative colitis, in increased risk for colorectal cancer. Improving medication adherence in patients is an important challenge for physicians. Understanding the different patient types, the reasons given by patients for non-adherence, simpler and more convenient dose regimens, dynamic communication within the healthcare team, self-management package incorporating enhanced patient education and physician-patient interaction and identifying the predictors of non-adherence, will help devise suitable plans to optimize patient adherence.

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