

Special Article - Inflammatory Bowel Disease

Adherence to Treatment in IBD Patients

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Abstract

Crohn's Disease and Ulcerative Colitis are chronic diseases with a relapsing-remitting course that require long-term treatment, not only to induce remission, but also to prevent relapses and further complications. Adherence to treatment is not always optimal in patients with chronic diseases and this may affect disease outcome and lead to increased health care costs because of the risk of disease flares, medication escalation and complication rates. For this purpose, some tools are useful to help health-care professionals to improve patient's medication adherence. The best strategies include education, use of reminder systems and greater involvement of dedicated professionals, like IBD nurses. The next challenge will be to incorporate these strategies into daily clinical practice.

Keywords: Inflammatory Bowel Disease; Adherence; Ulcerative colitis; Crohn's disease

Abbreviations

IBD: Inflammatory Bowel Disease; CD: Crohn's Disease; UC: Ulcerative Colitis; MMAS: Morisky Medication Adherence Scale; 5-ASA: 5-aminosalicylic Acid; anti-TNF: Anti-Tumor Necrosis Factor; PSST: Problem Solving Skills Training.

Introduction

Crohn's Disease (CD) and Ulcerative Colitis (UC), commonly known as Inflammatory Bowel Disease (IBD), include chronic conditions with a relapsing-remitting disease course. The aetiology is multifactorial with both genetic and environmental factors, contributing to disease pathogenesis [1].

These disorders typically affect young adult subjects who usually need long-term treatment, not only to induce remission during flare-ups, but also to prevent relapses and/or further complications [2].

As in other chronic diseases, adherence is not always optimal in patients with IBD and it is therefore important to teach awareness regarding the importance to adhere to a specific therapy and cure program.

Adherence has been described as the extent to which a person's behavior (in terms of taking medication, following diet, or changes in lifestyle) corresponds to the recommendations and instructions given by a health care provider. The term comprises two dimensions, compliance and persistence, which include the capacity of the patient to follow advices for the whole period of prescription. The implication for the patient implies that he is free to decide whether to adhere or not to the doctor's recommendations thus enriching the definition of compliance with special emphasis on the need for agreement. Disobedience and blame are therefore no longer considered in the term adherence and patient empowerment and physician responsibility are in focus in the process of cure.

How to measure adherence

Adherence can be measured using different tools, *objective and direct* such as the measurement of drug concentration in biological

fluids or the direct observation of the patient, or *indirect* using questionnaires, patient diaries, pills counters, clinical evaluation, electronic monitoring, or number of prescription refills [3,4]. Each method has advantages and disadvantages. While direct approaches are expensive, burdensome to the healthcare provider, and susceptible to distortion by the patient, indirect methods are easier to use but more susceptible to misrepresentation and the healthcare providers could overestimate patient's adherence [3].

Data from the American Heart Association shows a progressive decrease in adherence starting with not filling the prescription (12%), filling the prescription but not taking the medication (12%) to taking the medication but not being persistent with it (29%). Moreover, among the patients who take their medications, 22% take less number of drugs than what is prescribed. So as per the database, only 25% of those who are prescribed a medication actually take it like they should [5].

Studies regarding IBD from Europe, North and South America show excellent adherence rates in clinical trials, but unfortunately outside this setting, adherence seems to be poor. However, the percentage of patients classified as non-adherent varies greatly among the studies. Most studies reported that between 30% and 45% of the patients were non-adherent. Different tools were used to measure adherence: self-report (interviews, questionnaires, visual analogue scales, diaries), blood analysis, urine analysis, and pharmacy refill. In 4 of the studies non-adherence, measured through a biological assay, was about 9% – 13%; whereas most studies using questionnaires, interviews, or visual analogue scales reported rates between 30% and 43% [6].

Non-adherence can be *intentional* when the patient personally decides not to adhere to a cure program or *accidental* when the intention to adhere is conserved but some practical issues interfere with adherence, such as forgetfulness [7].

It's also important to specify that adherence is generally superior in patients with acute vs chronic conditions requiring long-term therapies and periodic medical appointments: in these patients, a

progressive reduction in therapy assumption has been described after 6 months from starting therapy [3].

We should also consider that the management of any chronic disease is related to the concept of *self-management* which includes multiple domains, unique to each patient, rather than involving the healthcare provider-patient relationship, or the social environment where the patient's lives in.

How to predict non-adherence

The management of IBD includes lifestyle changes, everyday intake of oral medications, periodic subcutaneous injections or infusions, surgical procedures, and endoscopic/radiological examinations.

The self-management of these conditions can be difficult and associated with poorer mental and physical health outcomes. In contrast, effective self-management can improve disease outcomes as measured by fewer symptoms, fewer hospitalizations, and less need for medical treatment escalation [8].

For these reasons, physicians should be able to identify risk factors associated with non-adherence and find practical strategies to enhance awareness among IBD patients.

Coenen et al. evaluated predictors of low adherence in a Belgian IBD population, observing that patients younger than 40 years, who were single using mesalamine doses and unemployed in spite of having a good educational background were poorly adherent, whereas being self-employed was associated with good adherence [9].

Another important aspect influencing adherence derives from a good communication-relationship between the patient and the physician. Linn et al, investigated the amount of information that each patient remembers at the end of a follow-up visit. In this study 68 IBD patients were interviewed by a nurse team immediately after they left the physician's office and after 3 weeks. Patients were asked about the name and the dosage of each drug prescribed the purpose of the therapy, duration, and frequency of the treatment. The questionnaire administered at the end of the visit revealed that the patients could refer only 52.6% of the information received during the visit and 53.85 of them remembered the doctor's prescription after 3 weeks [10].

These data demonstrated that limited knowledge about IBD medication and inappropriate self-perceptions of illness play a significant role in increasing medication non-adherence, underling an unmet need in the educational program [11,12].

The most common reasons for non-adherence result from practical or perceptual barriers [10]. Practical barriers could be related to forgetfulness (difficulties in remembering to take the medication) or the inability to integrate the medication regimen in their daily life (working duties, difficult modality of administration, multiple dosing of the drug). Perceptual barriers may derive from the personal belief about the need to take the medication (feeling good) and fears of concern regarding the medication (adverse events) [13-16].

Adherence related to type of treatment

Unfortunately, non-adherence, which is observed for any type of medication, can have bad consequences for the patient's health status

[17,18]. Mesalamine, one of the drugs more frequently prescribed to IBD patients, is the index therapy for many adherence studies.

In a study conducted on UC patients in Canada, adherence to mesalamine was measured using the medication possession ratio. The results showed 38% to 68% medication possession rate and the percentage was highly dependent on the type of mesalamine. The same study also analyzed persistence to the different 5-aminosalicylic acid (5-ASA) treatments showing 45.5% persistence over 12 months [18].

Moreover, Kane et al. in a self-reported adherence survey found that rates of non-adherence to medication, measured with Morisky Medication Adherence Scale (MMAS), were sub-optimal and that non-adherent behavior could have a negative impact on disease activity, increased rate of complication and health-care cost. This study was conducted in a group of 150 outpatients, 47% assuming 5-ASA, 54% immunomodulators, 15% infliximab, 8% injectable biologic, and 6% budesonide. Results showed that 34% of patients were poorly adherent (with a MMAS score of <6), 38% were moderately adherent (with a MMAS score between 6 and 8) and only 28% were highly adherent (with a MMAS score of 8) [17]. Another study quantified the costs of non-adherence in 12.5% higher than the annual healthcare costs [19].

The importance of the formulation too, makes a difference: pills are more difficult to be taken at work or can be difficult to swallow, while enemas can cause abdominal pain/discomfort or can be difficult or impractical to use [13].

As far as biological therapy is concerned, non-adherence may range from 17% to 45%. Again, non-adherence is associated with higher rate of hospitalizations and increased healthcare costs [20]. In a recent prospective multicenter study, the overall non-adherence rate for anti-TNF agents were 25% and this rate was higher for adalimumab (33%) than for infliximab (24%). This can be due to the self-administration of adalimumab at home with respect to the intravenous administration of infliximab which needs a hospital visit. Moreover, non-adherence to anti-TNF agents, was strongly associated with loss of response to anti-TNF agents. Longer intervals between outpatient clinic visits (\geq three months) and limited knowledge of the prescribed medication were found to be significant predictors of non-adherence [21].

Selinger studied 356 IBD patients, 268 of them were on 5-ASA (35,1% Non-Adherent), 131 on thiopurines (18,3% Non-adherent) and 54 on biologics (7,4% Non-Adherent). This study showed that adherence was significantly higher with more aggressive therapies. Data showed that adherence - measured with Medicine Adherence Report Scale was significantly lower in patients treated with 5-ASA than in those treated with thiopurines or with biologics (16.8 ± 4.0 vs 18.2 ± 2.0 vs 19.3 ± 0.0 ; $p < 0.0001$). Moreover, patients on thiopurines were more likely to be non-adherent for the fear of adverse events while patients on 5-ASA were more likely to be non-adherent also for a lower belief in the necessity to take their medications [22]. Furthermore, Bager et al. recently found the lowest medication adherence rates in patients treated with 5-ASA. In this study, adherence to therapy was measured by means of an anonymous electronic questionnaire which was administered to 300 IBD patients recruited from the outpatient

clinic at a tertiary hospital in Denmark within a period of four months during 2014. Data showed that among patients treated with 5-ASA, those who had active disease were more adherent than those with an inactive disease. In contrast, disease activity in patients treated with more aggressive therapies (thiopurines, steroids, biologics) did not affect medication adherence. Non-adherent patients, who considered medication to be less important, had more difficulty in remembering to take the medications, and felt less confident taking the medication than adherent patients [23]. These issues could be related to poor awareness of the disease, its treatment and the patient's need to be more involved in decision making regarding their daily medical treatment. For these reasons, it is necessary that patients are conscious of their disease and the risks of low medication adherence, that can ultimately improve their participation in decisions regarding treatment and cure programs [24].

A Portuguese study conducted among a group of 112 outpatients who were under the medication of azathioprine, out of which 49.1% also received concomitant biological therapy, showed that about 70.5% of patients adhered to thiopurines. A similar adherence rate was found between patients treated with infliximab (68.4%) while adherence to combination therapy was as high as 72.7%. It is important to realize that about 30% of the patients did not adhere to immunosuppressors. Moreover, this study highlighted that perceived importance of maintenance treatments, balanced against concerns regarding side effects. This perception remained as a determinant in influencing patients, to take their drugs. This suggests that it is mandatory to spend more time discussing safety in the immediate as well as long term, along with the expected benefits of any treatment [25].

Feagan et al. compared healthcare costs for patients who were adherent to infliximab therapy and for patients who were intermittently adherent. Intermittent adherence was defined as having therapy for a clinically significant period but with missed doses. This behavior may have various reasons: patients can increase intervals between infusions because they suffer from infections or if they travel to work, far from the infusion center, but sometimes they forget the date of the infusion or they take holidays. Adherence to therapy was associated with less cost with respect to intermittent adherence. The total costs of adherent patients beside the biologic were significantly lower for adherent (\$13,097) vs intermittently adherent (\$20,068) patients [26].

Finally, adherence can be perceived differently by patients and their doctors. A questionnaire was administered to 449 patients and to 76 gastroenterologists, who were asked to give their opinion about adherence in their patients. Doctors perceived adherence as adequate in 75% of the patients while the patients' evaluation using the Morisky Medication Adherence Scale reported a 44% of low adherence. Lack of persistence was reported in 22% of the patients receiving conventional treatment, while a lower percentage (14.9%) was encountered in patients receiving biological therapies and reasons for interrupting biologics were mostly shared with the physician due to adverse events or to remission [27].

Strategies to improve adherence

To reduce rates of non-adherence, it is important to develop solutions that improve physical and mental health outcomes and

reduce healthcare utilization. Strategies should be focused on telemedicine and the use of technology, such as messaging systems on smart phones, auditory reminder systems, sound pill containers that can provide the patient with specific information about which medication is to be taken at any given time. Another useful strategy is the use of Problem Solving Skills Training (PSST) through which individuals are encouraged towards a more positive and rational approach to solving problems and overcome adherence barriers [28]. Moreover, healthcare professionals must take careful efforts in considering the quality of the communication with the patients, paying special attention to the patient's level of knowledge about the therapy and its risks and benefits [28-30]. It would be important to create a multidisciplinary team with psychologists and IBD nurses to design the appropriate process of care for each patient.

Patients evaluate the role of nurses in disease management positively and emphasize the confidence and peace of mind they have in being treated by nurses [31].

Conclusions

Poor adherence increases health care costs because of the increased risk of disease flares, medication escalation and complication rates. Most studies reported that non-adherence can be as high as 45%, the main reasons being both intentional and accidental, or sometimes related to patient's belief about the disease and its treatment.

The best strategies aimed at reducing accidental non-adherence include education and use of reminder systems; in contrast to, strategies that ameliorate intentional non-adherence include Problem Solving Skill Training and greater involvement of dedicated professionals like IBD nurses. An accurate assessment of adherence should be carried out with tailored interventions in relation to the specific barriers.

To promote adherence to treatment among IBD patients is a challenge for healthcare providers. Routine clinical practice needs to be incorporated for new strategies to improve adherence in IBD patients now, more than ever as we face high costs of the new and more expensive drugs used for the cure of IBD.

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