REVIEW ARTICLE

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Strategies to Improve Adherence and Outcomes in Patients with Ulcerative Colitis

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Contents

Abstract

This review examines studies of patient adherence to 5-aminosalicylic acid therapy conducted outside the context of a controlled therapy trial, considers the reasons why patients do not adhere to their medication and its consequences, and interventions to improve adherence and disease outcomes. Non-adherence in the inflammatory bowel disease population tends to mirror other chronic illnesses, in the range of 40–60%. Factors that appear to affect adherence include younger age, single status, heavy pill burden, perception of lack of benefit and feeling uninformed about the effect of medication. Three important outcomes of non-adherence include increased risk for disease activity, increased healthcare costs and the possible increased risk of dysplasia/colorectal cancer. Strategies to improve adherence include patient education and 'health literacy', along with discussing patient misperceptions and fears on an individual basis, decreasing the daily regimen and switching to high-dose formulations, and incorporating patient self-management techniques into practice.

The standard first-line treatment for the induction and maintenance of remission in patients with mild to moderate ulcerative colitis (UC) is 5-aminosalicylic acid (5-ASA).[1] Its mechanism of action is thought to involve inhibiting a number of anti-inflammatory processes acting at the level of the colonic mucosa.[2] The aminosalicylates have been shown to inhibit production of interleukin-1 and tumour necrosis factor-α. 5-ASA is a potent inhibitor of both the cyclo-oxygenase and lipoxygenase pathways, as well as being one of the most potent known free radical scavengers and antioxidants.[2] 5-ASA also inhibits activation of nuclear factor-κB (NF-κB), a central transcription regulatory factor involved in the inflammatory process and detected

in cells from inflamed mucosa of patients with UC.[3]

There are several different 5-ASA delivery systems available (including both oral and rectal formulations) that all share the same aim, namely to achieve maximal drug delivery to the colon, while minimizing systemic absorption. Oral 5-ASA therapies are recommended over topical therapies as the first-line treatment of both left-sided and extensive mild to moderate UC because they have shown efficacy in treating the entire large intestine.[1,4] For mild to moderate distal disease, a combination of topical and oral 5-ASA therapy is recommended.[1,4]

This review looks at the problem of low levels of adherence in patients with UC, the reasons behind this and suggests solutions for improving adherence. Although there are numerous different 5-ASA delivery systems, currently there does not appear to be an agent that confers less of a risk of non-adherence than the others.

1. Non-Adherence in Ulcerative Colitis

Patient adherence can be defined as the extent to which a person's behaviour is in accordance with the instructions given by their health practitioner. Although adherence is known to be low (in the range of 50%) in other chronic diseases, such as hypertension, diabetes mellitus and asthma,[5] there are few data published about the level of outpatient adherence in UC outside of the clinical trial setting.

A small number of studies have been conducted, using various methods, to investigate the level of adherence in patients with UC in the 'real world' environment. In a cohort study of 92 patients with clinically inactive disease who were followed-up for more than 48 weeks with appointments occurring every 12 weeks, 43% of patients were found to be 100% adherent, while in the remaining 57% of patients adherence did not fall below 95%.[6] However, patients consented to being studied, so it is likely that they did not truly reflect 'real world' behaviour. An earlier study by van Hees and van Tongeren[7] assessed adherence to sulfasalazine therapy by measuring the levels of sulfapyridine in patients' serum, as a marker for metabolized sulfasalazine, in 51 patients shortly before and 1–6 months after discharge from hospital. Upon questioning, the majority of patients claimed that they were adherent; however, approximately 41% of patients were found to have serum sulfapyridine levels substantially below that prior to discharge and, thus, were considered to be non-adherent.

In a cross-sectional prevalence study from central England, Stone et al.[8] reported on 344 patients with inflammatory bowel disease (IBD) from a population of approximately 87 000. From database information, utilization of 5-ASAs by practitioners was only 65% and good adherence to 5-ASA therapy (defined as consumption of >80% of medications) by patients was only 42%.

Previously, the group at the University of Chicago studied 99 UC patients in remission, examining their prescription refill information as a measure of adherence.[9] It is thought that the objective nature of pharmacy data provides a more accurate reflection of possible medication consumption outside of the structured clinical trial environment. In this study, the authors found that only 40% of patients were adherent and the median amount of medication consumed was 71% of the dose prescribed.

Qualitative research conducted on adherence reveals that patients strike a balance with perceived necessity versus concern for adverse events, development of immunity to therapy, the impact of active symptoms and the willingness to self-medicate.[10] Moshkovska et al.[11] also used structured interviews to assess patient adherence to 5-ASA therapy. They found that the amount of information the patient possessed and the perception of benefit of 5-ASA therapy drives adherent behaviour.

2. Factors Affecting Adherence

It is important for physicians to understand the patient characteristics that may be associated with a risk of non-adherence. The previous study identified a list of patient characteristics that correlated with adherence and non-adherence (table I).[9]

Patient non-adherence is more likely to be a problem during periods of disease remission because there are no clinical symptoms to act as a

Table I. Patient characteristics found to correlate with adherence and non-adherence from prescription refill information from a cohort study[9]

Factors associated with adherence	Factors associated with non-adherence
Being married	Being single
Having more extensive disease	Having left-sided disease
Having had a recent colonoscopy	Being prescribed four or more concomitant medications
	Being male

reminder to take medication. At these times, rather than continuing on the prescribed regimen, patients often adjust their medication by taking it less frequently than instructed, altering the dose from that prescribed, taking it only when they feel unwell or forgetting to take their medicine at the scheduled time.[12] However, this 'forgetfulness' may often be linked to a form of disease-denial – they are in remission and do not wish to be reminded of their status as a person with a disease while they feel well.

Many factors associated with non-adherence are financial, emotional or treatment-related, rather than being disease-related. When patients are questioned, they give many reasons for non-adherence. These include heavy pill burden, unclear treatment regimen, forgetfulness, financial burden, lack of adequate information and lack of support.[12]

The Manitoba Inflammatory Bowel Disease Cohort Study also investigated the nature of adherence in patients with either Crohn's disease or UC. Patients from this population-based cohort were queried by postal questionnaire regarding adherence to a range of therapies to treat IBD.[13] A total of 35% of patients met the study's criteria for low adherence. Males with UC were significantly more likely to have poor adherence than males with Crohn's disease ($p < 0.01$). In this study, the investigators found that age was a predictive factor for adherence in females; younger females were less adherent than older females. Males of all ages had comparable levels of adherence and the rate of poor adherence in males was broadly similar to that of the older women (which was a novel finding and contrasted from the results of our previous study where younger males were the least adherent). Other factors contributing to poor adherence in the Manitoba Cohort study were heavy pill burden and frequent administration, which are similar findings to previous studies. However, the main factors were found to be cost (reported by 25% of patients), reinforcement of status as person with a disease condition (13%), unpleasant adverse effects (13%) and lack of belief in the effectiveness of the medication (12%).

The only other study that examined non-adherence with medications in UC other than 5-ASAs was by Cerveny et al.[14] Fifty-six percent of patients admitted to non-adherence, and there was no difference between the sexes, diagnoses or marital status for a higher risk of non-adherence. Thirteen percent of patients prescribed 5-ASA had undetectable 5-ASA urine metabolites.

Other studies with large pharmacy databases have identified several factors associated with short- or long-term persistence with 5-ASA medications. In the short term, all prescribed 5-ASA products had equal adherence rates at 3 months, which ranged from 72% to 82%,[15] and refill rates from a large pharmacy warehouse showed a sharp decline to 60% for all 5-ASA formulations after only 3 months' use.[16] Risk factors for long-term non-adherence, according to pharmacy refill rates, included male sex, presence of a co-payment and use of a mail order prescription service.[17]

3. Adherence and Outcomes

The clinical outcomes of non-adherence can be detrimental to patients. It has been shown that there is a correlation between poor adherence and increased frequency of relapses. In the previously described cohort of patients collected by Kane et al.,[18] clinical outcome was measured prospectively. Multiple Cox proportional hazards model revealed that patients who were not compliant with medication had more than a 5-fold greater risk of recurrence than the compliant patients (hazard ratio 5.47; 95% CI 2.26, 13.22; $p < 0.001$). Non-adherent patients were found to have more than a 5-fold increased risk of disease relapse (61% chance) compared with those who were adherent (11% chance; $p = 0.001$). As part of the study, non-adherent pa-

tients were asked why they were not taking their medications.[9] The majority stated that they simply forgot one of their doses. Fewer than 10% of patients reported adverse effects and cost.

In a cost-effectiveness study, the Maryland BlueCrossBlueShield database was utilized to analyse cost of care for UC.[19] Adherence to prescribed medications was linked to outpatient visits, tests, Emergency Department and inpatient services. Non-adherence was associated with a 30% increase in out- and inpatient costs per year compared with those patients who refilled greater than 80% of their prescription medications.

There are now several studies that suggest that documented medication consumption is protective for colon cancer, which is an important concern for the long-term natural history of UC. Moody et al.[20] studied 168 patients with UC diagnosed between 1972 and 1981, and correlated sulfasalazine non-adherence with risk of colorectal cancer. A patient was classified as non-compliant if there was clear evidence in the medical record of medications not taken or upon the advice of a physician that medication was discontinued. Their crude colectomy rate was 23% in 10 years, with a 3% rate in those patients on maintenance sulfasalazine and 31% in patients who were either non-compliant or not receiving all medications. Because the authors found a colectomy rate and cancer incidence similar to previously published series, they concluded that medications were beneficial in reducing cancer risk. In a second retrospective case-control study, Pinczowski et al.[21] found that a record of at least a 3-month history of therapy with sulfasalazine had a protective effect for colon cancer. There was a 62% reduction in risk with any history of therapy in the 102 patients studied. However, it is difficult to interpret this finding because documentation of dose and duration of therapy for each patient was imprecise.

Eaden and colleagues[22] found in a case-control study that mesalamine at a dose of 1.2 g/day or greater reduced colorectal cancer risk by 91% in patients with UC compared with no treatment. There was also a protective effect of visiting the physician more than two times per year, but the same was not found for the number of surveillance colonoscopies. More data on mesalamine comes from investigators at Mount Sinai in New York who followed patients with UC which was indeterminate for dysplasia.[23] Those patients receiving 5-ASA ≥2 g/day did not progress to definite dysplasia, suggesting that any chemoprotective effect occurs early in the cancer progression pathway. Rubin and colleagues[24] reported the University of Chicago experience with all forms of 5-ASA in UC patients. The use of at least 1.2 g/day of a 5-ASA carried a 76% relative risk reduction for the development of colorectal cancer when controlled for disease extent, duration and folic acid use. In contrast, IBD patients receiving 5-ASA agents who were followed-up in Canada did not appear to have the same protective effect.[25] A recent meta-analysis by Velayos et al.[26] demonstrated a 50% reduction in risk for dysplasia or colorectal cancer in those patients who had a history of regular 5-ASA use.

4. Strategies for Improving Adherence

The fact that there is conflicting evidence about the most at-risk populations suggests that the problem of poor adherence is a multifaceted issue. A patient deciding not to take their medication is a common problem that physicians may not fully understand because many patients are reluctant to discuss, or give inaccurate representations of, their adherence levels. The risk of problems with adherence is likely to increase when there is a poor relationship between the patient and physician.[27] If patients do not feel comfortable with their physicians, do not trust them or do not feel they are being taken seriously, they may be less likely to follow the physicians' recommendations. Patients also need to understand the continuous requirement for the medication because if they do not, they are less likely to take it in the correct manner. A recent study by Davis et al.[28] found that approximately half of patients could not read at least one of five labels on pill bottles. This concept is commonly referred to as 'health literacy'. Therefore, to help improve adherence, physicians need to make efforts to connect with their patients and ensure they understand their

medication instructions. Only by listening to patients' medication-related problems, not being judgmental and being prepared to suggest alternative therapies, can they effectively gauge adherence levels.

Since pill burden and multiple-daily dose administration have been shown in some studies to be associated with non-adherence, formulations that require less frequent and/or fewer doses may assist in improving patient adherence. A recent systemic review of interventions to enhance adherence to medications in chronic illnesses found that the only consistent success rates have been with those that aim to simplify the dose administration regimen.[29]

In 1985, Dickinson et al.[30] asked the question whether continuous sulfasalazine was necessary in patients with quiescent UC. A randomized trial of continuous or on-demand sulfasalazine for patients with UC was conducted in this small pilot study. Of the 18 patients in the 'on-demand' group who were directed to take sulfasalazine 3 g/day starting within 24 hours of symptom recurrence, seven relapsed within the study period, four within the first 2 months of the trial. Three of ten patients randomized to the continuous group relapsed. Adherence was measured by serum sulfapyridine levels every 4 months for 1 year or until relapse, and was reported as adequate for patients in both groups. The authors concluded that because there was no difference in relapse rates between the two groups and because serological testing showed sulfapyridine levels to be therapeutic, an 'on-demand' regimen may be as efficacious as continuous therapy. These results were published as preliminary and, unfortunately, to date, no larger studies have been published that corroborate these results.

More recently, Bardazzi and colleagues[31] in Italy conducted a maintenance trial in 50 patients. Patients who were receiving 5-ASA 2.4 g for the first 7 days of each month were compared with those receiving 5-ASA 1.6 g/day and assessed every 2 months. Intermittent treatment yielded a 71% remission rate versus 66% in the continuous group, which was not found to be significantly different. Because of the small size of this study, no definitive conclusions could be made. In 1999, Ardizzone et al.[32] asked if maintenance therapy was always necessary. 112 patients with UC who had been in remission for at least 1 year were randomized to mesalazine delay release (Asacol®) 1.2 g/day or placebo, stratified by the length of remission. In those patients who had been in remission for 1–2 years, Asacol® [1] was significantly better than placebo in maintaining remission; however, interestingly, in the patients who had been in remission longer term (median length 4 years), there was not the same benefit.

These studies, while intriguing, are older and were performed before our understanding of the potential importance of mucosal healing. It may be true that a patient in remission for >4 years is not in need of maintenance therapy, but that is a very small subset of patients.

Several mesalamine formulations have recently been licensed or are in late-stage development. They are designed to maximize medication delivery in a convenient administration regimen. These formulations include a newly developed Multi Matrix System® (MMX®) formulation, higher-dose mesalamine tablets and micropellet sachets. MMX® mesalamine (Lialda™, also known as Mezavant XL™ in the UK and Ireland, and as Mezavant™ elsewhere), a high-strength formulation using MMX® technology designed to provide prolonged release throughout the entire colon,[33] was licensed in the US in early 2007 for the induction of remission of active, mild to moderate UC. MMX® mesalamine has been the first therapy in placebo-controlled clinical trials to demonstrate efficacy in mild to moderate UC when given once or twice daily in a divided dose.[34,35]

Asacol® high-dose (800 mg) tablet has been tested as a formulation that reduces the number of total tablets required per day and recently received US FDA approval.[36,37] Salofalk Granu-Stix® and Pentasa® sachets of micropellets are designed to be easy to swallow and, thus, enable patients to take large doses at a time and reduce the need for fre-

1 The use of trade names is for identification purposes only and does not imply endorsement.

quent dose administration. A once-daily Pentasa® sachet formulation is currently in phase III clinical trials.[38]

As many patients do not adhere to their treatment regimen, there is a strong case for attempting to improve adherence by simplifying the administration regimen. As pill burden and frequent (or 'confusing') administration regimens are the most consistent issues raised by patients who are non-adherent, newer therapies that require fewer administration occasions per day and/or reduce the number of tablets to be taken on each occasion may prove successful for improving adherence.

One pilot study assessed patients' adherence levels to once-daily versus twice- or three-times-daily administration with mesalamine.[39] The study followed 22 patients with quiescent UC over a 6-month period, who were randomized to receive mesalamine either once daily or the conventional administration frequency of two or three times per day. Adherence was assessed using the prescription refill method of previous studies and was defined as a rate of >80%. A good tolerability profile is suggested because there was no obvious difference between the two groups in terms of adverse clinical outcomes. Interestingly, the overall medication consumption was higher in the once-daily administration group for the short-term but consumption equalized with time. A subsequent study suggested that once-daily Asacol® for 12 months was as safe and efficacious as twice or three times daily.[40] However, perhaps the most important finding from this study was that regardless of regimen, total medication consumption over time was the greatest predictor of a favourable outcome.

These data suggest that patient education does not necessarily have to focus on dose administration frequency, but rather on the importance of regular consumption and its benefits. The importance of continuous medication must be stressed, and physicians would need to be confident that switching patients from one 5-ASA therapy to another will improve treatment efficacy and not simply create a new situation for non-adherence. One study assessed efficacy while switching.[41] However, in this study, the change in formulation was to a less convenient administration regimen and, therefore, the impact of switching on adherence cannot be considered. The study was carried out in nine UC patients who were prone to relapse (defined in this study as a UC Disease Activity Index [UC-DAI] endoscopy score of ≥2). Patients were changed from routine oral Asacol® therapy (2.4 g/day administered as two tablets, three times daily), to Pentasa® microgranules (4 g/day, given as two tablets, four times daily). A significantly lower ($p = 0.013$) mean UC-DAI score was observed after 12 weeks following switching (6.81 ± 0.72 vs 8.18 ± 0.58).

Efficacy has also been assessed in patients switched to a once-daily 5-ASA formulation. The results of this study showed that MMX® mesalamine 4.8 g/day was effective for providing clinical and endoscopic remission in patients with active, mild to moderate UC who had transferred directly from low-dose (≤2.0 g/day) oral 5-ASA therapy. Since this formulation had the convenience of once-daily administration, the improvement in efficacy may also be matched by increased adherence rates.[42]

These studies suggest that changing a patient's regimen to a different formulation can prove to be efficacious. Larger studies need to be carried out to assess the effects of changing therapies to a formulation with less frequent dose administration on patient adherence levels in a community setting.

5. Methods to Optimize Adherence

Optimizing adherence is most effective when open lines of communication characterize the relationship between physician and patient. Allowing the patient the time to voice his concerns and questions is the first step in effective education. Open-ended questions during a patient visit can be time consuming, but setting an appropriate tone so as not to overestimate the patient's level of education is paramount in establishing a good relationship. One study from the psychology literature featuring IBD patients revealed that, when asked, their greatest concern was the uncertain nature of their disease.[43]

In addition, patients expressed a significant concern about the effect of medications on their disease.

It has been suggested that physicians may overestimate patient comprehension in regard to instructions and education. Martin and colleagues[44] showed that of IBD patients who had been surveyed, 62% of UC patients felt ill informed about their disease. Although 86% of patients who responded knew of the increased risk of cancer, only 44% knew that it was possible to screen for dysplasia and possible prevention of invasive cancer. Other literature also suggests that non-adherence is linked to patient non-comprehension.[45]

A new model of patient adherence has been proposed in which effective patient-physician dialogue is central to promoting patient adherence.[46] This theoretical framework is, in part, supported by findings that higher patient-physician discordance has been associated with unfavourable health outcomes as well as with decreased patient satisfaction, a variable that is related to poorer adherence. In a study of 153 patients, the non-adherence rate for IBD medications within 2 weeks of a clinic visit was 41%.[47] A total of 81% of these patients were found to have 'non-intentional' non-adherent behaviour (i.e. forgetfulness or carelessness in taking medication). Intentional non-adherence was found to be associated with patients who were considered 'non-distressed' by psychosocial measurements but showed high discordance with their physician in terms of disease activity. The clinical implications of these findings suggest that the therapeutic relationship can influence adherence just as much as individual clinical and psychosocial characteristics.

Patient autonomy is also a means to enhance adherence with medications. Realizing the potential difficulties for long-term adherence with sulfasalazine, Dickinson et al.[30] studied continuous versus 'on-demand' sulfasalazine in 28 patients with quiescent UC. This patient-centred, self-management approach offers the opportunity to improve outcomes through patient education and empowerment. In a British study, 203 patients with UC were randomized to either routine treatment by a specialist or patient-centred self-management in the primary care setting.[48] Patient training included a written algorithm for treatment and a 15–30-minute training session. In the self-management group, relapses were treated significantly more rapidly than in the conventional group (14.8 vs 49.6 hours; $p < 0.01$), had fewer office visits (0.9 vs 2.9/year; $p < 0.01$) and the length of the flares that did occur was shorter.

6. Conclusions

Medication non-adherence is prevalent in chronic illnesses and UC is no exception, as outlined by repeated studies showing >40% non-adherence rates. The problem is still not well understood because it is difficult to predict who and when non-adherence becomes a clinically important issue. As discussed in this article, there is emerging data to show the long-term benefits of adherence and the risks of non-adherence with medications or other physician recommendations. Through physician and patient education, the clinical relevance of adherence can be emphasized and disease outcomes will be improved in the long term.

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