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Systematic review: impact of non-adherence to 5-aminosalicylic acid products on the frequency and cost of ulcerative colitis flares

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SUMMARY

Background
Ulcerative colitis (UC) can be maintained in remission with 5-aminosalicylic acid (5-ASA) medications, but frequent non-adherence by patients who are feeling well has been associated with more frequent flares of colitis.

Aim
To perform a systematic review of the published literature and unpublished randomized clinical trials (RCTs) regarding the impact of non-adherence with 5-ASA medications on the incidence of UC flares and costs of care.

Methods
A search of MEDLINE, EMBASE and the Cochrane databases was performed. Prospective studies of UC maintenance with 5-ASAs in adults were selected if they included data on adherence and disease flares. Studies using insurance claims data to estimate the impact of non-adherence on cost of care were included. Data from unpublished RCTs were obtained from the FDA with a request under the Freedom of Information Act.

Results
The relative risk for flare in non-adherent vs. adherent patients ranged from 3.65 to infinity. Data were obtained from six unpublished 5-ASA RCTs, but none measured the impact of adherence on disease activity. The comorbidity-adjusted annual costs of care in adherent patients were 12.5% less than in non-adherent patients, despite increased medication expenditures.

Conclusions
A substantial proportion of UC flares and medical costs of UC are attributable to 5-ASA non-adherence. As non-adherence to 5-ASA medications is common, cost-effective strategies to improve adherence are needed. The impact of adherence on disease activity should be measured in RCTs of all inflammatory bowel disease treatments.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic medical condition which, barring colectomy, requires life-long prophylactic medical maintenance therapy. The first-line therapy for UC of mild or moderate activity is 5-aminosalicylic acid (5-ASA). Both oral and topical formulations are available to deliver 5-ASA directly to the site of disease activity. Most available oral formulations require multiple daily doses with multiple tablets per dose. Such regimens are inconvenient and can interfere with normal daily activities of patients and reduce overall quality of life. The additional burden of a complex and inconvenient dosing regimen can have a negative impact on adherence to treatment in a range of clinical settings and can result in poorer long-term outcomes.[1–6] This is particularly true in chronic medical conditions such as UC, where patients require lifelong medical therapy, even during periods of symptomatic remission (quiescence). 'Real-world' adherence rates for patients with chronic medical conditions requiring long-term pharmacotherapy are generally estimated to be approximately 50%[7] and may be as low as 30% for certain disease states.[8] In clinical trials, the impact of the daily dosing regimen on adherence is one of the few factors that has been quantitatively measured, demonstrating that adherence decreases significantly (89% vs. 65%, $P < 0.001$) when the frequency of daily dosing of medication is increased from q.d.s. (once daily) dosing to t.d.s. (thrice daily) dosing.[9]

While adherence to treatment with 5-ASAs in clinical trials has been excellent, studies have shown that adherence to prescribed 5-ASA therapy outside this setting is poor.[10–18] Patient non-adherence to prescribed 5-ASA therapy has been associated with an increase in the risk of symptomatic relapse, leading to a decrease in quality of life and an increase in accrued societal and personal costs.[19] In contrast, patient adherence to prescribed 5-ASA regimens has been shown to have long-term benefits and may be associated with a decreased risk of colorectal cancer.[20–24]

Despite these data, the magnitude of the effect of non-adherence on disease outcomes in UC remains unclear. Multiple randomized controlled trials (RCTs) have been published about the efficacy of 5-ASAs for the maintenance of UC remission and many of these trials have been submitted to the Food and Drug Administration (FDA) as part of new drug applications (NDAs). Although publication of these RCTs did not quantify the impact of adherence on frequency of UC flares, we hypothesized that data submitted to the FDA would quantify this. Therefore, we sought to obtain this information through requests under the Freedom of Information Act to the FDA.

No previous systematic review has described the published literature and the unpublished RCT data regarding the impact of non-adherence with 5-ASA medications on the incidence of flares of disease. Also, no systematic review has quantified the impact of non-adherence on the costs of UC care. Our hypothesis is that documented non-adherence to therapy is associated with significantly increased disease activity and increased net medical costs. Our goal was to quantify the increase in UC flares among non-adherent UC patients vs. UC patients adherent to 5-ASA medications and to quantify the impact of non-adherence on cost of UC care.

MATERIALS AND METHODS

Literature search

A computer-assisted search in MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE and the Cochrane Library was conducted to identify potentially relevant published papers. A search of the MEDLINE database from 1950 to September 2007 was performed using the following exploded (exp) medical subject headings (MeSH) and textwords (.mp): (exp Aminosalicylic Acids/ OR exp Mesalamine/ OR (mesalazine or Mesalamine).mp OR (5-aminosalicyl$ or 5-asa).mp OR (asacol or pentasa or salofalk or rowasa or asamax or canasa or SPD476 or; lialda or mezavant or mesasal or claversal or azulfidine).mp OR Sulfasalazine.mp. or exp Sulfasalazine/ OR (olsalazine or Dipentum).mp OR (balsalazide or colazide or colazal).mp) AND (exp inflammatory bowel diseases/ or exp colitis, ulcerative/ OR (ulcerative adj1 colitis).mp) AND (exp Patient Compliance/ OR exp Treatment Refusal/ OR adhere$ or comply or complian$ or non?adhere$ or non?complian$.mp. Identical search terms were used to search MEDLINE In-Process and Other Non-Indexed Citations and the Cochrane Library.

A search of the biomedical and pharmaceutical EMBASE database from 1980 to September 2007 was performed using the following exploded (exp) medical subject headings (Emtree) and textwords (.mp): (exp Aminosalicylic Acid Derivative/ OR exp Mesalazine/ OR (mesalazine or Mesalamine).mp OR (5-aminosalicyl$ or 5-asa).mp OR (asacol or Pentasa or Salofalk or Rowasa or Asamax or Canasa or SPD476 or Lialda or

Mezavant or Mesasal or Claversal or Azulfidine).mp OR exp Salazosulfapyridine/ OR Sulfasalazine.mp OR exp Olsalazine/ OR (olsalazine or Dipentum).mp OR exp Balsalazide/ OR balsazide or Colazide or Colazal).mp) AND (exp Ulcerative Colitis/ OR exp enteritis/ OR ulcerative adj1 colitis.mp.) AND (exp Patient Compliance/ OR (adhere$ or comply or complian$ or non?adhere$ or non?complian$).mp. Results from the four searches were merged and duplicates removed.

Additional searches of the Digestive Disease Week and United European Gastroenterology Week abstracts from 2003 to 2006 were performed with the search terms 'adherence' OR 'compliance' AND 'ulcerative colitis'. Similar hand searches of the abstracts from the American College of Gastroenterology and Crohn's and Colitis Foundation of America (CCFA) meetings were performed for the years 2003–2006. The Web of Science, Conference Papers Index and ISI Proceedings databases were also searched for relevant abstracts. Manual searches of reference lists from potentially relevant papers were also performed to identify any additional studies that may have been missed using the computer-assisted strategy.

In August 2007, we submitted a Freedom of Information Act request to the US FDA. We requested NDAs for drugs approved for the maintenance of UC remission [i.e. mesalazine (mesalamine) (Asacol, Procter & Gamble, Cincinnati, OH, USA) and olsalazine (Dipentum, Alaven Pharmaceutical, Marietta, GA, USA)] and for any other drugs that have been reviewed for this indication.

Study selection criteria

Two investigators (P.H., D.R.) independently reviewed the titles and abstracts of all citations identified by the literature search. Potentially relevant studies were retrieved and the selection criteria applied. The selection criteria were: (i) prospective study of UC maintenance treatment; (ii) adult patients (children's adherence may be influenced by parents); (iii) disease activity or flare or costs were measured in an objective and reproducible fashion; (iv) adherence was measured in a reproducible fashion;[25] (v) minimum of 90 (median) days of follow-up; (vi) adherence was measured without knowledge of disease activity or cost outcome and (vii) results were reported as raw numbers for each level of disease activity, divided into subgroups by level of adherence. Similar criteria were applied to the RCT data provided by the FDA in response to our request under the Freedom of Information Act. Any prospective or retrospective study using insurance claims data to estimate the impact of non-adherence on cost of care was included.

Data extraction and data analysis

Eligible articles were reviewed in a duplicate, independent manner by two investigators (P.H., D.R.). Agreement between investigators was >95%, and disagreement on data fields was resolved by consensus. For each study, the following information was extracted: study design, inclusion and exclusion criteria, duration of follow-up, study sponsorship, method of measurement of adherence, definition of levels of adherence, method of measurement of disease activity and definition of levels of disease activity. If available, the methods used to measure the following additional outcomes were extracted: costs, steroid use, colectomy, hospitalizations, time to flare, the total number of subjects, age, gender, extent of disease, duration of disease, median baseline severity and concomitant medications. The total number of subjects in each level of adherence, the number having a flare and data from other outcomes (costs, time to flare, hospitalization or colectomy, steroid use) were recorded for each study. Data on adherence and on disease flare frequency were obtained from each maintenance study submitted to the FDA for these medications.

Data on covariates or subgroups that affected the likelihood of flare were also extracted. The data obtained from these original research articles describing the effect of 5-ASA adherence of disease activity in UC, were tabulated and presented in a descriptive form. Given the variability of the methods and patient samples of the studies included, no attempt was made to perform a meta-analysis or to stratify by the quality of each individual study.

RESULTS

Characteristics of selected studies

Searching the MEDLINE, EMBASE and Cochrane Library databases yielded 246 articles, and the abstracts search yielded 113 abstracts using the above-described search strategies. Reviews of the titles and abstracts of the 359 total publications identified 51 potentially relevant articles. Review of the full manuscripts of these 51 articles yielded six articles or

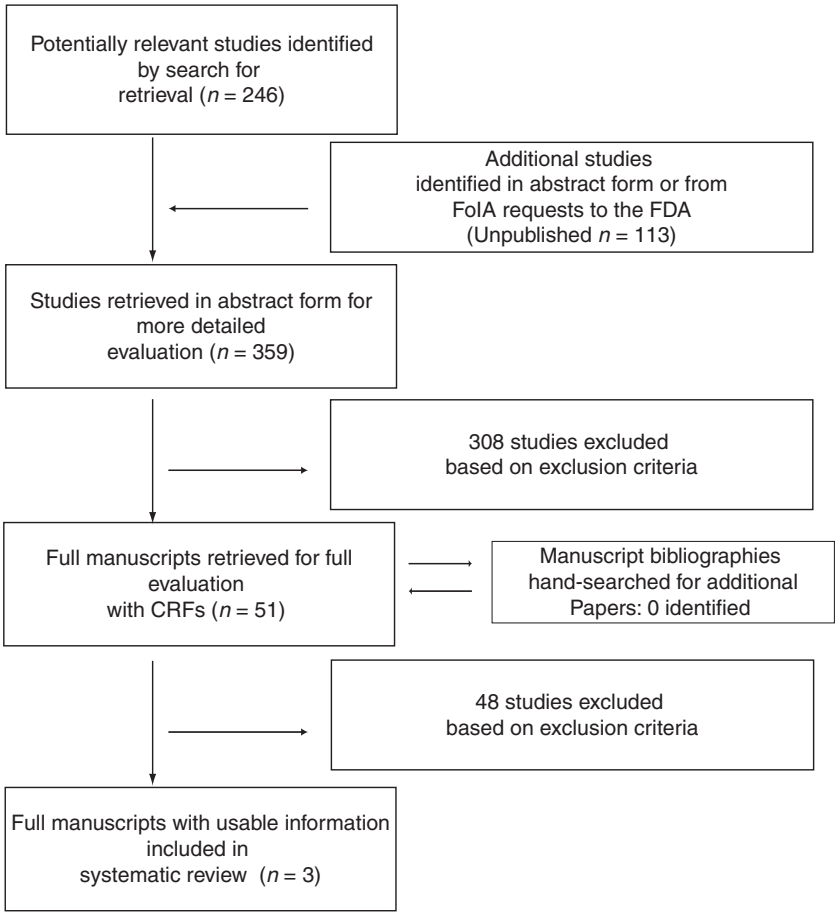

Figure 1. Search results: studies of the impact of adherence on ulcerative colitis flare.

abstracts that met our criteria. Three of these studies were excluded from the data tabulation because they appeared to be describing the same data set as a previous publication by the same authors. The results of the searches and screening are presented in Figure 1.

Additional study data were collected through requests under the Freedom of Information Act to the FDA. These yielded data from four (C.1, C.2, C.6, C.15) maintenance studies of mesalazine (Asacol) and two (84E012, 84E024) maintenance studies of olsalazine (Dipentum).

Excluded studies

A number of studies that addressed adherence in inflammatory bowel disease (IBD) were excluded from our detailed review. None of these linked adherence to outcomes, which was the primary reason for their exclusion. Two studies used open-ended questions to ask patients about adherence issues and the ideal medication. Hall *et al.*[26] learned from focus groups that major issues included not being sure maintenance medications were needed, fears of side effects, fear that they would develop 'immunity' to oral medications, and fear of drug interactions. Loftus' survey[27] identified the characteristics of an ideal IBD therapy as: high efficacy, no side effects, oral dosing, low cost, few pills and less frequent dosing.

Several studies evaluated the incidence of IBD medication non-adherence and the associated risk factors. Van Hees and van Tongeren in 1982[17] found that 41% of out-patients on sulfasalazine had drug levels significantly lower than they had at discharge and 12% of out-patients had undetectable levels. Klugmann *et al.* in 1990[28] found that 63% of a cohort on sulfasalazine were non-adherent by serum measures of drug. In 2003, Sewitch *et al.*[14] found that 61/153 patients reported non-adherence (35% of these were intentional). Factors associated with non-adherence included short disease duration, mild disease activity, uncertain if medication would help and discordant relationship with the physician. Shale and Riley in 2003[13] found that 43% reported non-adherence to mesalazine in a sample of 98 IBD patients, with associated predictors of t.d.s. dosing, full

employment and depression. Lopez *et al.*[12] reported 35% intentional non-adherence and 72% overall non-adherence in 40 subjects with associated factors including low Inflammatory Bowel Disease Questionnaire (IBDQ), quiescent disease, lack of trust in medical care and long duration of disease.

Bokemeyer[29] looked specifically at non-adherence to thiopurines, with 6-tioguanine (thioguanine) levels as the gold standard. Six of 81 out-patients were non-compliant by this measure. Bernal *et al.*[15] found 43% non-adherence to IBD medications in a 214 patient cohort, with 45% of all mesalazine doses missed. More adherent patients had complex, steroid refractory disease and were more likely to have hospitalizations, surgery or infliximab use. Cerveny *et al.*[30] found 36% noncompliance in 177 IBD patients with increased noncompliance in those who had perceived previous medication adverse effects and those who considered themselves well-informed about IBD. More recently, Ediger *et al.*[10] found 30% non-adherence in a cohort of 326 IBD patients with slightly different predictors of non-adherence in men and women. For men, having UC and being fully employed were risks for non-adherence. In women, being young, not on immunosuppressants and rating low on agreeableness were risk factors. Reported obstacles to adherence included cost, that taking medications reminds that they have a chronic illness, side effects and uncertainty that medication actually helps. Bertomoro *et al.*[31] found 39% non-adherence in a cohort of 475 IBD patients. Risk factors included young age, recent diagnosis, full time employment, rectal therapy and multiple daily doses.

Results have been similar, if not more discouraging, in two paediatric studies. Mackner and Crandall[32] found 52% of children and 62% of adults reported non-adherence in 50 families with family dysfunction and poor child coping predicting non-adherence. Oliva-Hemker *et al.*[33] evaluated a strict adherence definition of taking 80% of the prescribed medication and found 50% non-adherence with azathioprine and 66% with mesalazine in a study of 51 children. Strikingly, an emergency department visit in the past 6 months increased adherence ninefold. An IBD educational intervention study by Waters *et al.*[34] in 69 IBD patients produced a nonsignificant trend towards increased adherence.

Impact of non-adherence on flare frequency

Two prospective studies of patients receiving maintenance treatment of UC with 5-ASA medications addressed the impact of non-adherence on the frequency of flares in UC. The results of these studies are summarized in Figures 2 and 3.

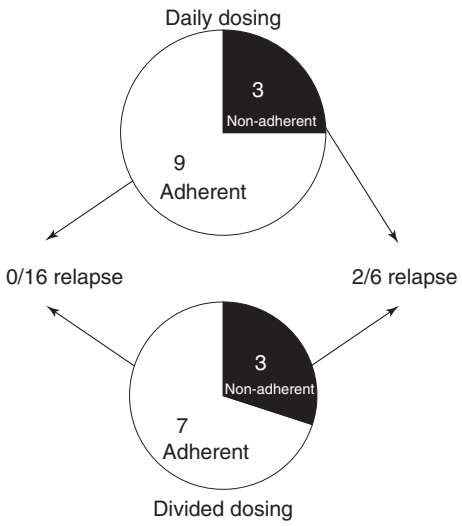

Figure 2. The relapse rate is presented stratified by adherence status and dosing regimen in Kane's pilot study.

The first was a pilot study by Kane *et al.* published in 2003.[35] In this study, 22 patients with quiescent UC were prospectively enrolled in a study comparing daily (12 subjects) and conventional divided dosing (10 subjects) of 5-ASA medications. Subjects were excluded for immunomodulator use, hospitalization, steroid use, significant symptoms in the previous 4 months, a history of irritable bowel syndrome, a history of *Clostridium difficile* infection or current use of antidiarrhoeal medication. The subjects were 82% female, with an average age of 40 years and an average time in remission of 10 months. The average 5-ASA dose was 2.6 g daily and the conventional dosing patients were either on three times daily (3) or twice daily (7) dosing regimens.

Adherence was defined prospectively as a rate of medication consumption of greater than 80% of the prescribed regimen, determined through contacting patient pharmacies. A relapse of disease was defined prospectively as a score of >3 points on a modified Harvey–Bradshaw Index.[36] At 3 months of follow-up, adherence was improved in the daily-dosing regimen group vs. the conventional dosing regimen group (100% vs. 70%, $P = 0.04$) and no disease relapses occurred. At 6 months of follow-up, no significant difference in adherence was detected between the daily-dosing regimen group vs. the conventional dosing

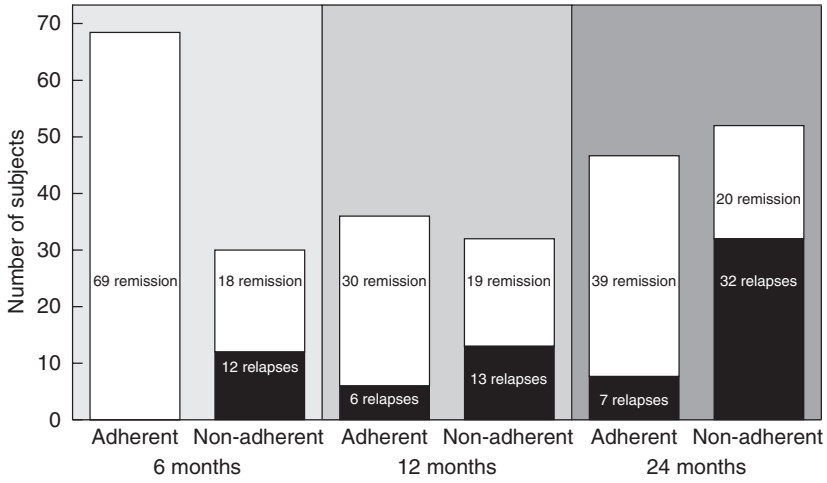

Figure 3. The relapse rate by adherence status at 6, 12 and 24 months in Kane's cohort study. Note the growing number of subjects becoming non-adherent over time and the subsequent increase in relapses of disease activity.

regiment group (75% vs. 70%, $P = 0.80$) when adherence is defined as consumption of >80% of medication each month, although this study was underpowered to detect a difference in adherence of <30%, assuming 70% adherence in the conventional dosing group.

Total medication consumption was also measured and the total amount of medication taken at the 6 month mark trended higher in the daily-dosing regimen compared with the conventional dosing regimen (90% vs. 76%, $P = 0.07$). At the end of the trial, patients in the daily-dosing regimen tended to be 'very satisfied' with their treatment regimen compared to patients in the conventional dosing regimen (83% vs. 60%, $P = 0.18$).

None of the 16 (0%) adherent subjects experienced a relapse of UC. Two of the six (33%) non-adherent subjects experienced a relapse of UC. The relative risk of relapse associated with non-adherence in this study was infinite.

In a second study by Kane *et al.*,[19] a cohort of 99 UC patients in remission were prospectively followed up for 24 months. Subjects were recruited at the University of Chicago Medical Center, if they had been quiescent for 6 months, maintained with mesalazine and had verified UC. Subjects were excluded, if they had been hospitalized in the previous 12 months, required steroids or immunomodulators in the past 6 months or ever had surgery for UC. The median age was 42, the median duration of UC was 8 years and 52 of 99 subjects were male.

Adherence was defined prospectively as a rate of medication consumption of more than 80% of the prescribed regimen. This was calculated from pharmacy records, as the number of days' supply of medication obtained in a 6-month period prior to evaluation, divided by the number of days in the 6-month period, multiplied by 100 to produce a percentage. A recurrence of disease was defined as the occurrence of urgency, bleeding or pain with four or more bowel movements per day.[37] Data were provided on all 99 subjects at 6 months, 86 remaining subjects without a flare at 12 months and 67 without at flare at 24 months. Three subjects did not complete the study, one because of loss to follow-up, one because of death unrelated to UC and the other because of proctocolectomy for dysplasia.

At 6 months of follow-up, none of the 66 (0%) adherent subjects experienced a recurrence of UC. Twelve of the 30 (40%) non-adherent subjects experienced a recurrence of UC. The relative risk of recurrence associated with non-adherence at this time point was infinite. One hundred per cent of the flares that occurred over 6 months were associated with non-adherence.

After 12 months of follow-up, 54 subjects were adherent and 32 were non-adherent. Six of the 54 (11.1%) adherent subjects experienced a recurrence of UC. Thirteen of the 32 (40.6%) non-adherent subjects experienced a recurrence of UC. The relative risk of recurrence associated with non-adherence at this time point is 3.65 (95% CI: 1.54–8.67). After 24 months of follow-up, 39 subjects were adherent and 28 were non-adherent. One of the 39 (2.6%) adherent subjects experienced a recurrence of UC. Seven of the 28 (25%) non-adherent subjects experienced a recurrence of UC. The relative risk of recurrence associated with non-adherence at this time point is 9.75 (95% CI: 1.27–74.9).

Eighty-two per cent of the flares that occurred over 2 years were associated with non-adherence. Adherent subjects had an 89% chance of maintaining remission, while only 39% of non-adherent subjects remained in remission over this 2-year study. Most subjects who flared did so within 1 year of onset of non-adherence. None of the patients who flared required hospitalization or colectomy for flare, although five of 39 required initiation of steroids, two of 39 required rectal therapy and the remaining 32 of 39 required an increase in their 5-ASA dose. Seventy subjects responded to questioning about why they were non-adherent: 50% attributed it to forgetfulness, 30% to too many pills and 20% decided that they did not really need the entire amount of medication prescribed. A multivariate analysis of factors associated with disease recurrence over 24 months identified non-adherence [hazard ratio (HR): 5.5] as the leading factor for disease recurrence. Remission longer than 1 year (HR 2.7), disease duration of less than 5 years (HR 2.4) and family history of IBD (HR 2.4) were also significant factors that predicted disease recurrence.

Impact of non-adherence in unpublished RCTs

Through Freedom of Information Act requests to the FDA, four studies of maintenance with mesalazine (Asacol) and two studies of maintenance with olsalazine (Dipentum) were identified in NDA files. Non-adherence did occur in these studies, but non-adherence was a justification for removing the subject from the study in each of these trials. The definitions of non-adherence varied from trial to trial, but all studies removed any subject that met the definition for non-adherence. Among patients who did not meet the prespecified definition of non-adherence, no additional data about level of adherence with study medication were provided. Intention-to-treat (ITT) analyses were presented, but the effects of non-adherence vs. adherence on efficacy in the treatment arm were not presented. Further data were not recorded for non-adherent subjects. Therefore, no data extraction about the impact of non-adherence on UC flares could be performed with these studies.

Impact of non-adherence on costs

Only one study focused on the net costs of non-adherence in UC patients being treated with 5-ASA medications. Kane *et al.*[38, 39] performed a retrospective analysis of the Maryland CareFirst Blue Cross Blue Shield (BCBS) database for the years 2002–2004 to determine the association between 5-ASA adherence and health care costs. Subjects were included if they had an ICD-9 diagnosis of 556 (UC) and were continuously enrolled in the insurance plan throughout the study period. Ongoing 5-ASA users (with 5-ASA prescriptions filled in the first 3 months of the study) were excluded to enrich for new 5-ASA users. The 4313 selected subjects had a mean age of 47.3 years and 58% were female. Mesalazine was used by 71.2%, sulfasalazine by 16%, balsalazide by 7.5% and olsalazine by 2.3%. Pharmacy charges for 5-ASAs billed to the BCBS database were used to calculate the medication possession ratio (MPR). The MPR is the ratio of the number of days' supply of drug obtained to the number of days in the study period. Persistent subjects were defined as those with an MPR ≥0.8. Subjects who failed to refill their medications or switched to a different 5-ASA were considered nonpersistent.

Pharmacy 5-ASA charges for 5-ASAs billed to the BCBS database were used to classify the study subjects as nonpersistent (they stopped 5-ASA or switched to a different 5-ASA during the study period) or persistent (persisted in 5-ASA use through the end of 2004). The overall persistence rate over 3 years was 57.2%. The highest rate of persistence was seen in sulfasalazine users (64%), who also had the highest MPR of 0.82, which may be explained by the fact that generic sulfasalazine had the lowest co-pay (the nuisance fee paid by patients each time a medication is dispensed) in this insurance plan. There were no differences in persistence by gender, but subjects aged 18–39 years (54%) and 40–64 years (57%) were less persistent than subjects aged under 18 years (65%) or over 64 years (59%).

Persistent patients had 49.8% lower unadjusted total medical costs, a difference of $1875 US per year. A multivariate model was used to adjust for covariates including age, gender and the Charlson Comorbidity Index. While the adjusted medication costs were 6.9% higher for adherent patients, the adjusted overall medical costs were 12.5% lower for persistent vs. nonpersistent patients.

DISCUSSION

Our systematic review found that only two prospective studies quantified the impact of non-adherence on frequency of UC flares. The increased risk of UC flares associated with non-adherence is quite wide

with relative risks ranging from 3.65 to infinity. This wide range is likely because of small sample sizes. For reasons of limited data, we sought unpublished RCT data for 5-ASA medications approved for maintenance of UC remission. However, past RCTs have not measured the impact of non-adherence on frequency of UC flares. We think that adherence data are a valuable secondary endpoint and that adherence should be measured in future prospective maintenance studies. Nevertheless, the available data suggest that a significant proportion of disease flares in UC patients may be attributable to non-adherence with 5-ASA medications. Our systematic review also demonstrates that only one study has assessed the economic impact of non-adherence on UC management and found that adherence with 5-ASA medications appears to lower the cost of UC management despite the increased costs of medication. This seems to occur because improved adherence with 5-ASA medications minimizes UC flares and the high costs associated with managing these flares. As non-adherence is common in UC patients, cost-effective strategies to improve adherence are needed and we recommend that interventions to improve adherence including simplification of daily dosing regimen, lowering patient costs (including co-pays), educational programs for UC patients and incentives to facilitate physician–patient communication should be studied in controlled trials.

Adherence is particularly difficult to measure, given that patients who are monitored are more likely to act in a desired manner (the 'Hawthorne effect'). By convention, adherence is defined as the consumption of at least 80% of prescribed medicine over a specified period of time (usually 1 year for chronic conditions). Some authors use the term 'partial adherence' for those patients who are adherent for a portion of the time period or for a chosen cut off point, but this leads to confusion and not used by the majority of investigators in this field. Unfortunately, there is no gold standard method for measuring either compliance or adherence, as different therapies lend themselves better to specific measurements than others. Medications with discrete therapeutic serum levels are therefore much easier to manage (e.g. phenobarbitol, phenytoin) than therapies without. Historically therefore, compliance has been measured by pill count, but this does not take into account the factor of persistence over time. Patients could also foil the system by disposing of pills prior to a visit requiring the pill count. Currently, electronic monitoring is considered the best method for tracking medication taking behaviour during controlled trials. This method not only determines not only how often a patient takes his/her medicine but also what time of day and has the ability to track individual trends in behaviour. The downside to this technology is its cost, which prohibits its use for individual patients in clinical practice. In the clinical practice setting, the use of pharmacy records to track refills has been found to be effective. However, this can be time-consuming for a single practitioner and patients may refill prescriptions from multiple pharmacies or large pharmacy wholesalers that automatically send out refills at scheduled times, obviating the need for a patient to call and initiate the refill.

Our systematic review demonstrates that relatively little data are available about the impact of non-adherence on UC management. We were surprised that only two prospective studies have reported the increased risk of UC flares associated with non-adherence. With limited data, it is not possible to quantify precisely the magnitude of this increased risk. We were also surprised that only one economic study using insurance claims has assessed the impact of non-adherence on costs of UC management. Finally, we were dismayed that previous RCTs, which established the efficacy of 5-ASAs for maintenance of UC remission, did not measure the impact of non-adherence on UC flares. As non-adherence in IBD therapy is common and important in reducing therapeutic efficacy, it could be argued that a true ITT analysis would include non-adherent patients as treatment failures or would continue to follow these patients to report the frequency of UC flares. As the existing data are so limited, future IBD therapeutic trials should evaluate and report the effect of non-adherence (if it occurs in a clinical trial) on the efficacy of the therapy. This would provide prospective data to advise patients on the importance of high levels of adherence with particular therapies and might justify measures to increase adherence in therapies whose efficacy is very sensitive to non-adherence. Similarly, this endpoint could also reveal the minimum effective dosing schedule for maintenance of remission, enabling more streamlined and potentially more convenient dosing. Unfortunately, data gathered in prospective RCTs of new therapies, with motivated subjects and study coordinators, are likely to include artificially high adherence rates, which will not reflect real-world

adherence. More real-world, pragmatic maintenance studies are needed to define truly the modifying effect of adherence on efficacy of each IBD therapy.

Given the limited literature on the effects of non-adherence to 5-ASA medications on UC disease flares, future efforts should focus on pragmatic, real-world studies of disease maintenance to examine the relationship between adherence and disease activity with all forms of IBD medical therapy. Ideally, these studies will: (i) occur in a 'real world' setting to gauge true adherence and its impact outside of clinical trials; (ii) account for a variety of important patient-specific, disease-specific and medication-specific variables (age, gender, cost of medication to the patient, recent disease course including hospitalizations, steroid use and rectal therapy, duration of disease, immunosuppressant use, employment status, dosing regimen and depression); (iii) collect disease activity data prospectively, with validated measurement tools like the Simple Clinical Colitis Activity Index; (iv) collect adherence data prospectively and report the effect of non-adherence in varying degrees on the efficacy of the therapy to review the minimum effective dosing schedule for maintenance of remission and (v) follow patients over an extended time period of a year or more to detect longer-term outcomes including steroid use, hospitalizations and colectomy. This type of pragmatic maintenance study may be particularly important in the future for biological therapy for IBD, as it is not yet known whether self-administered biologics will have similar non-adherence problems in real world settings and episodic non-adherence could lead to rapid loss of efficacy of biologies. One challenge that needs to be overcome in the proposed prospective maintenance study design is the problem of notifying patients that their adherence to therapy is being measured during the informed consent process without biasing the results. However, if successful, collecting this information could change our current understanding of how non-adherence modifies the real-world efficacy of medications in UC.

Our systematic review highlights the dearth of economic data about the impact of non-adherence on UC flares and this is another topic that should be assessed within larger maintenance studies that examine the relationship between adherence and disease activity. Only the study by Kane *et al.*[38, 39] has assessed this topic finding that adherence was associated with lower total medical costs despite higher medication costs. This finding is not surprising as advocates of value-based insurance designs[40, 41] have shown that high medication co-pays can result in poor adherence and net increases in medical costs in diabetes. It appears possible that a zero co-pay or even pay for adherence (P4A) might be cost-effective in UC, as has been suggested through Markov models of different co-pay strategies for the use of angiotensin converting enzyme inhibitors in diabetes.[42] Given these data, it appears that investment in interventions to improve adherence may be beneficial for patients and cost-effective for insurers.

This review also raises the question of what interventions would improve outcomes for patients and would be cost-effective for insurers. Levy and Feld's[43] review of adherence-improvement strategies in gastroenterology treatment highlight the importance of: (i) the patient's understanding of the benefits of adherence; (ii) a supportive environment and a strong relationship between the physician and patient;[44] (iii) specific adherence assignments that the patient commits to; (iv) reduction in barriers to adherence (costs, inconvenience); (v) reminders to adhere; (vi) monitoring adherence and (vii) rewards for successful adherence.

Many of the factors that have been shown to affect adherence rates are difficult to modify (Table 1), including age, gender, diagnosis, recent disease course, immunomodulator use (if required for remission), previous adverse events attributed to medication, agreeableness and education level.[10, 11, 13, 14] However, changes in the cost of the medication to the patient (e.g. switching patients to generic sulfasalazine or lowering co-pays for other medications), enhancement of the patient–physician relationship, simplification of

Table 1. Factors affecting adherence to 5-ASAs in ulcerative colitis

Risk factors that are difficult to modify	Potentially modifiable risk factors
Age	Cost of co-pay and other barriers to refilling medications
Gender	Treatable depression
Patient agreeableness	Physician–patient relationship
Education level	Dosing regimen
Recent disease course	
Immunomodulator use (if required for remission)	
Previous adverse events attributed to medication	

the dosing regimen (once vs. twice or thrice daily) and treatment for depression (if present) could be tested as interventions to improve adherence in UC.

There is some evidence that interventions can affect adherence to 5-ASAs in UC. A one-time, information-based intervention in which patients were given an opportunity to share their reasons for non-adherence and were reminded of the benefits of adherence led to adherence (defined as >80% pharmacy fill rate – the percentage of monthly prescriptions actually dispensed to the patient) over the next 6 months in 10/21 previously non-adherent patients.[44] However, a recent systematic review concluded that the intervention with the biggest impact on medication adherence is reduction in daily dosing regimen.[45] Studies that have used electronic monitoring to measure adherence in chronic disease states including hypertension,[46] angina[47] and diabetes[48] have consistently found significant adherence benefits from daily vs. twice- or thrice-daily dosing. Compared to alternatives including changes in patient's medication co-pay, educational efforts to improve patient adherence and inducements to enhance physician communication with the patient, simplification of the dosing regimen is likely the easiest intervention to accomplish.

In summary, this systematic review has identified a lack of economic data on impact of non-adherence on costs of UC care, a lack of data on the impact of non-adherence on frequency of UC flares and the lack of controlled trials which assess the impact of interventions to improve adherence in UC. Based on the limited data available, adherence to 5-ASA medications decreases the frequency of UC flares and simple interventions to increased adherence are likely to be cost-effective. Therefore, effective interventions to improve adherence to these medications are clearly needed. Ideally, non-adherence risk scores to identify patients at high risk of non-adherence can be developed and validated to target adherence interventions to the patients who need them most. Further studies to identify and develop effective interventions to improve adherence in patients with UC are necessary.

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