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Adherence to 5-Aminosalicylic Acid Treatment in Ulcerative Colitis

Love BL[1,2*], **Johnson J**[2], **Hardin JW**[3], **Schulz R**[1]

[1]*Department of Clinical Pharmacy and Outcomes Sciences, South Carolina College of Pharmacy, Columbia, SC, USA*

[2]*At the time of writing: William J. Bryan Dorn Veterans Affairs Medical Center, Columbia, SC, USA*

[3]*Arnold School of Public Health, University of South Carolina, Columbia, SC, USA*

[*]**Corresponding Author:** Love BL, SC College of Pharmacy, 715 Sumter St., CLS 314D, Columbia, SC 29208; Tel: 803-777-5727; E-mail: loveb@sccp.sc.edu

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Abstract

Background: Oral 5-aminosalicylic acid (5-ASA) therapy is the first choice therapy for ulcerative colitis (UC), and adherence to therapy is important for long-term clinical improvement.

Objective: To assess the relationship between dosing frequency, pill burden, clinical outcomes and medication adherence in patients receiving various 5-ASA formulations. Methods: A single center, cross-sectional study was conducted in outpatients diagnosed with ulcerative colitis and prescribed aminosalicylates during a 3.5 year period. Medication adherence was quantified using the medication possession ratio (MPR), and non-adherence was defined as taking less than 80% of the prescribed dose. Demographic data, 5-ASA medication fill history and treatment outcomes data were collected. Clinical outcomes were assessed including surgery, hospitalization, emergency department (ED) visit, and documented flares. Logistic regression was used to model the odds of adherence to 5-ASA based on medication and dosing frequency.

Results: Non-adherence was observed in 66 (52.4%) of the 126 enrolled subjects. The median adherence rate in all patients was 78.2% (IQR 39.3). Most patients received either balsalazide (38.9%) or mesalamine delayed release (DR) tablets [Asacol®] (31.8%). Very few subjects received 5-ASA once or twice daily (25.4%). Significant differences were observed between dosing frequency and daily pill burden when comparing "adherent" and "non-adherent"patients. Patients receiving mesalamine MMX [Lialda®], mesalamine DR, and sulfasalazine were more likely to be adherent compared to balsalazide. No significant association was noted between clinical outcomes and medication adherence.

Conclusion: Overall, medication non-adherence was common in this sample of patients. Less frequent dosing and choice of 5-ASA were associated with medication adherence in adjusted models.

Keywords Ulcerative Colitis; 5-Aminosalicylic Acid; Mesalamine; Balsalazide; Sulfasalazine; Medication Adherence

Abbreviations 5-ASA: 5-Aminosalicylic acid; UC: ulcerative colitis

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disorder primarily affecting the superficial layers of colonic mucosa. The annual incidence of UC in the United States is estimated to be 6-8 cases per 100,000 individuals [1]. Direct medical costs exceed $4 billion annually with medication costs totaling nearly $700 million [2]. UC accounts for approximately 250,000 physician visits and 30,000 hospitalizations annually. Treatment of UC is aimed at inducing and maintaining remission, improving quality of life, and decreasing the risk of complications of UC such as colorectal cancer [1,3].

The American College of Gastroenterology guidelines support oral 5-aminosalicylic acid (5-ASA) medications as the mainstay of treatment of UC. Several dosage forms and delivery systems are available to adequately deliver 5-ASA to the colon [1] Adherence to the prescribed 5-ASA regimen is important to maintain remission [3]. However, many of these formulations carry a large pill burden or require frequent dosing which can be an important barrier to medication adherence. Inadequate control of UC can lead to disease "flares" and reduced quality of life. Relapse of disease often leads to increased consumption of healthcare resources including hospitalization, ED visits, surgery, and addition of medication for disease control. As such, it is important that adherence is maintained even during periods of prolonged remission. In recent years, new formulations of 5-ASA with extended release formulation have been developed to decrease overall pill burden and dosing frequency in an attempt to increase adherence [4-6].

The aim of this study was to assess the relationship between dosing frequency, pill burden, clinical outcomes and medication adherence in patients receiving various 5-ASA formulations.

Methods

This study was a retrospective, cross-sectional study of adult veterans with a diagnosis of UC who received a 5-ASA prescription during a consecutive 3.5 year period. Patients with a diagnosis of Crohn's disease, irritable bowel syndrome, or other forms of colitis (i.e. microscopic or indeterminate colitis) were excluded. Additionally, any patients receiving infliximab, adalimumab, or certolizumab within 90 days prior to the initial prescription fill were excluded from the study.

The medication possession ratio (MPR), a widely used and validated proxy for medication adherence, was used to determine the percentage of time each patient "possessed" their prescribed 5-ASA medication within the study period. MPR was truncated at 1.0 for those patients with calculated MPR >1.0. Non-adherence was defined as MPR <0.8, and an adherence rate was calculated by multiplying MPR by 100%.

Statistical Analysis

Descriptive statistics were shown as n (%) for categorical variables and median (interquartile range). Categorical variables were compared using Pearson's chi-squared or Fisher's exact test. Continuous variables were described using nonparametric testing (Kruskal-Wallis and Mann-Whitney). We conducted a univariate logistic regression analysis to explore associations of factors related to aminosalicylate adherence. Variables with possible association with adherence ($p<0.2$) from the univariate analysis were entered into the initial multiple logistic regression model. A stepwise procedure was then followed for variable selection. The criterion to remain in the multivariate logistic regression model was set at $p<0.2$. All statistical tests were two-tailed, and statistical significance was defined as $p<0.05$. All data analyses were performed using Stata, version 12.1 (Stata Inc., College Station, Texas, USA).

Ethical Statement

The study protocol was approved by the WJB Dorn VA Medical Center Institutional Review Board and Research Review Board. The study met all criteria for Good Clinical Practice research.

Results

Subjects

A total of 308 patients who received a prescription for a 5-ASA medication between July 31, 2007 and December 31, 2010 were reviewed. Of these, 126 patients had a documented diagnosis of UC and were included in the analysis. Reasons for exclusion included Crohn's disease (n=74), microscopic colitis (n=26), and other unspecified forms of colitis (n=34).

In addition, a number of patients were excluded because they were receiving sulfasalazine for the treatment of rheumatoid arthritis rather than for the treatment of UC (n=48). The median adherence rate in all subjects was 78.2% with an IQR of 39.3. The median age was 64.2 years, and 95.2% were male.

The majority of patients received balsalazide capsules (38.9%) or mesalamine delayed release (DR) tablets [Asacol®] (31.8%). A minority of patients received 5-ASA at dosing frequencies less than or equal to twice daily (25.4%). Significant differences were observed between dosing frequency and daily pill burden when comparing patients categorized as "adherent" and "non-adherent".

There were no significant differences noted between clinical outcomes and medication adherence. Baseline characteristics of the final study sample are shown in Table 1.

Characteristic	All Patients N=126	Non-adherent (MPR <0.8) N=66	Adherent (MPR > 0.8) N=60	P-value*
Male, n (%)	120 (95.2)	61 (92.4)	59 (98.3)	0.12
Age, median (IQR)	64.2 (23.8)	62.6 (24.1)	64.6 (23.8)	0.17
Race, n (%)				
White	91 (72.2)	46 (69.7)	45 (75.0)	0.51
Black	25 (19.8)	16 (24.2)	9 (15.0)	0.19
Unknown	10 (8.0)	4 (6.1)	6 (10.0)	0.52
BMI, median (IQR)	26.9 (5.4)	27.2 (4.4)	26.7 (5.7)	0.18
Years since initial UC diagnosis, median (IQR)	5 (4)	5 (4)	6 (4.5)	0.31
Follow-up period [days], median (IQR)	776 (716)	864.5 (550)	565 (991)	0.08
Immunomodulator, n (%)	18 (14.3)	7 (10.6)	11 (18.3)	0.22
5-ASA medication, n (%)				
Balsalazide	49 (38.9)	32 (48.5)	17 (28.3)	0.02
Mesalamine (Asacol)	40 (31.8)	19 (28.8)	21 (35.0)	0.45
Mesalamine SA (Pentasa)	12 (9.5)	7 (10.6)	5 (8.3)	0.77
Mesalamine MMX (Lialda)	10 (7.9)	3 (4.6)	7 (11.7)	0.19
Sulfasalazine	15 (11.9)	5 (7.6)	10 (16.7)	0.17

Dosing Frequency, n (%)				
Once daily	4 (3.2)	1 (1.5)	3 (5.0)	0.35
Twice daily	28 (22.2)	7 (10.6)	21 (35.0)	0.001
Thrice daily	78 (61.9)	46 (69.7)	32 (53.3)	0.06
Four or more times daily	16 (12.7)	12 (18.2)	4 (6.7)	0.06
Daily pill burden, median (IQR)	6 (5)	9 (5)	6 (5)	0.02
MPR, median (IQR)	0.78 (0.39)	0.56 (0.27)	0.95 (0.12)	<0.001
* p-value reported compares baseline characteristics between non-adherent and adherent groups.				

Table 1: Baseline clinical characteristics for all ulcerative colitis patients stratified by medication possession ratio

Dosing frequency was inversely associated with medication adherence (Figure 1). Medication adherence in the once or twice daily group was statistically significant when compared to the three or more daily dosing group (p<0.001). Patients receiving balsalzide and mesalamine SA capsules had the lowest rates of adherence (MPR=0.67 for both). Conversely, the highest rate of adherence was observed in patients taking mesalamine MMX tablets (MPR=0.88; p<0.05 compared to balsalazide and mesalamine SA).

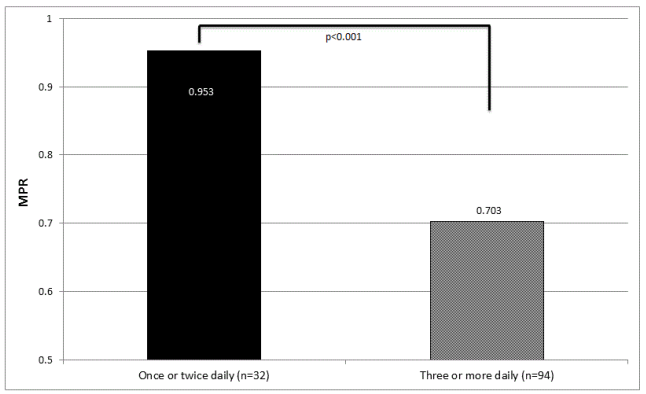

Figure 1: Median MPR stratified by 5-ASA dosing frequency

Logistic Regression Analysis

Based on the results of univariate logistic regression analyses, the following factors were included in the multivariate logistic regression analyses: male sex; age; black race; low BMI (25th percentile); immunomodulator use at baseline; drug and dosing frequency; and daily pill burden. Since drug regimen, dosing frequency, and pill burden are strongly linked, separate models were constructed modeling each of these factors separately (Table 2). Age, race, low BMI (<25th percentile), and immunomodulator use at baseline were included in the adjusted models. Patient's receiving medications three or more times daily were less likely to be adherent (aOR 0.19; 95% CI 0.07, 0.49). Compared to balsalazide, patients taking mesalamine MMX (aOR 5.71; 95% CI 1.20, 27.23), mesalamine DR (aOR 2.51; 95% CI 1.01, 6.25), and sulfasalazine (aOR 3.73; 1.05, 13.3) were significantly more likely to be adherent. A similar finding was observed with patients taking eight or fewer tablets daily (aOR 3.09; 95% CI 1.39, 6.87). We also evaluated the relationship between clinical outcomes (hospitalization, ER visits, and documented flares) and adherence, pill burden, and dosing frequency; however, none of these risk factors were significant in crude or adjusted models (Table 3).

	Medication Adherence (MPR>0.8)		Medication Adherence (MPR>0.8)	
Risk Factor	**cOR**	**95% CI**	**aOR**	**95% CI**
Dosing Frequency*				
Once or twice daily	Referent	-	Referent	-
Three or more daily	0.21	0.08, 0.51	0.19	0.07, 0.49
Drug				
Balsalazide	Referent	-	Referent	-
Lialda*	4.39	1.00, 19.20	5.71	1.20, 27.23
Pentasa	1.34	0.37, 4.88	1.49	0.39, 5.77
Asacol*	2.08	0.88, 4.89	2.51	1.01, 6.25
Sulfasalazine*	3.76	1.11, 12.8	3.73	1.05, 13.30
Pill Burden				
> 8 tablets/d	Referent	-	Referent	-
< 8 tablets/d*	2.69	1.28, 5.64	3.09	1.39, 6.87
aOR=adjusted odds ratio, adjusted for age, race, low BMI (< 25th percentile), and immune modulator use at baseline; 95% CI = 95% confidence interval for the odds ratio. * p< 0.05, adjusted odds ratio				

Table 2: Crude and adjusted logistic regression analyses examining relationship between medication related risk factors and adherence.

	Hospitalization (n= 17)				ER Visits (n= 19)				Documented Flare (n=46)			
Risk Factor	**cOR**	**95% CI**	**aOR**	**95% CI**	**cOR**	**95% CI**	**aOR**	**95% CI**	**cOR**	**95% CI**	**aOR**	**95% CI**
5-ASA Adherene												
MPR<80	Referent	-	Referent	-	Referent	-	Referent	-	Referent	-	Referent	-
MPR>80	0.56	0.19, 1.61	0.33	0.09, 1.30	0.99	0.37, 2.63	1.01	0.28, 3.61	1.14	0.55, 2.35	1.58	0.64, 3.88
Pill Burden												
>8 tablets/d	Referent	-	Referent	-	Referent	-	Referent	-	Referent	-	Referent	-
<8 tablets/d	0.73	0.26, 2.05	1.31	0.39, 4.37	0.43	0.16, 1.17	0.35	0.09, 1.36	0.56	0.26, 1.15	0.53	0.21, 1.35
Dosing Frequeny												
Once or Twice daily	Referent	-	Referent	-	Referent	-	Referent	-	Referent	-	Referent	-
Three or more daily	2.85	0.61, 13.2	2.1	0.33, 13.2	1.33	0.41, 4.34	0.42	0.08, 2.20	1.59	0.66, 3.82	0.98	0.33, 2.98

cOR = crude (unadjusted) odds ratio; 95% CI = 95% confidence interval for the odds ratio; aOR = adjusted odds ratio, adjusted for all other variables in the table in addition to age, race, low BMI (< 25th percentile), and immunomodulator use at baseline.

Table 3: Crude and adjusted logistic regression analyses comparing clinical outcomes (Hospitalization, ER visits, and Documented Flare) with medication factors.

Discussion

As hypothesized, an inverse relationship was observed between medication adherence and dosing frequency in our study. Less frequent dosing may improve medication adherence in ulcerative colitis as is seen with other chronic disease states, such as hypertension [7,8] and diabetes [9,10]. The benefits of less frequent medication administration on medication adherence and clinical outcomes have been demonstrated with mesalamine products traditionally dosed more frequently [11-13]. The overall low levels of medication adherence in our study are consistent with other retrospective claims database evaluations [14].

In addition, we found adherence to the mesalamine MMX (Lialda®) formulation was greater compared to other formulations. This formulation is intended for once daily dosing with a relatively low pill burden (median 2.5 tablets/day vs. 6.0 for all others; p<0.001). A high rate of medication adherence was also observed in the mesalamine DR and sulfasalazine groups. We believe that this occurred secondary to self-selection bias. Both products have been used clinically for inflammatory bowel disease for several decades. Within our study, patients taking sulfasalazine or mesalamine DR were likely taking them for an extended period of time with positive results. Balasalazide is also an older formulation; however, patients were more likely to be non-adherent to this drug. We believe that this occurred due to more frequent dosing and relatively high pill burden (median=9.0). Most patients were prescribed thrice daily dosing for balsalazide, whereas sulfasalazine was most often prescribed for twice daily dosing.

Increased symptoms due to disease activity are a strong predictor of low health-related quality of life scores, and reduction of symptoms can have a significant impact on QoL [15]. A variety of strategies have been proposed to reduce symptoms, including improving or maintaining medication adherence.16 Although there was no association between medication adherence and clinical outcomes in our study, previous work demonstrates a significantly increased risk of clinical relapse in patients with quiescent UC who are nonadherent [16,17]. In addition, daily 5-ASA dose (high vs. low) is not important when patients have a high to moderate level of adherence [18].

We acknowledge several important limitations with our study. First, this was single-center study conducted in a predominantly male veteran population. Patterns of adherence and clinical outcomes may differ in females or non-veteran populations. Secondly, the VA electronic medical record system allows for access to healthcare data within the VA system. Records are often unavailable for patients who receive care outside the VA system. Although the majority of our patients received all care within the VA system, any healthcare utilization in a non-VA setting may not have been captured resulting in an underestimate the number of clinical events during our study. In addition, severity of UC was unable to be accurately assessed at baseline using a validated scoring system (e.g. Montreal classification). Finally, a small proportion of patients were prescribed 5-ASA medications once daily during the study period; therefore, we were unable to assess this dosing frequency to the extent originally intended.

Adherence to commonly prescribed oral medications for UC is challenging for patients. Our findings suggest that prescribing 5-ASA with less frequent dosing and lower pill burden may improve adherence in ulcerative colitis patients. These factors did not translate into significant improvements in clinical outcomes in our study, possibly due to a small sample size.

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