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Determinants of Topical 5-Aminosalicylic Acid Use in Veterans with Ulcerative Colitis

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Abstract

Aims: The aim of our study was to identify the determinants of topical 5-ASA therapy in a large ulcerative colitis cohort.

Methods: We performed a cross sectional study of patients receiving care through the Veterans Administration (VA) from 2003 to 2009. Patients with UC were identified using ICD-9 codes. Patient demographic and prescription data were obtained from national VA datasets. Univariate and multivariate logistic regression were used to identify the effect of age, gender and race on topical 5-ASA therapy use.

Results: We identified 20,259 UC patients for inclusion in the analysis. The prevalence of topical 5-ASA therapy use was 27%. With univariate logistic regression, female gender and non-Caucasian race were associated with a higher odds of topical 5-ASA therapy use. Increasing age was associated with lower odds of topical 5-ASA therapy use. On multivariate logistic regression, Blacks and Hispanics remained more likely to use topical 5-ASA therapies compared to Caucasians and increasing age remained associated with a lower odds of topical 5-ASA therapy; however, other demographic features lost significance.

Conclusions: In a large, national cohort of patients with UC, Blacks and Hispanics were more likely to use topical 5-ASA therapies compared to patients of other ethnicities.

Keywords: Inflammatory bowel disease; Ulcerative colitis; 5-Aminosalicylic acid

Abbreviations: Inflammatory bowel disease (IBD); Ulcerative colitis (UC); 5-Aminosalicylates (5-ASA); Veterans Administration (VA); Decision Support Systems (DSS)

Introduction

Topical 5-aminosalicylate therapies (5-ASAs) are efficacious, safe and cost effective treatments for ulcerative colitis (UC). Current practice guidelines from the American College of Gastroenterology recommend topical 5-ASA therapy use in mild to moderate distal UC [1]. Compared to placebo, 5-ASA therapy can improve the probability of symptomatic, endoscopic and histologic remission [2]. Topical 5-ASA therapy combined with oral therapy is superior to either alone. The addition of 5-ASA enemas to oral 5-ASA medications raises the percent reaching clinical remission from 43% to 64% [3]. Despite documented efficacy, the use of topical 5-ASA therapies is variable.

Data from the United States suggest approximately 53% of newly diagnosed patients with UC were prescribed a topical 5-ASA therapy [4]. Studies from Europe have reported a wide range of topical 5-ASA therapy use. From Spain, a survey based study found gastroenterologists commonly recommended topical therapies (74-81%) [5]. However, they did not report the prevalence of patients who actually followed these recommendations. In contrast, a study from a Swiss IBD cohort found only 7.8% of

patients with UC were prescribed topical 5-ASA therapies [6]. These studies highlight the wide variation in topical 5-ASA therapy usage, but do not address possible determinants of topical 5-ASA therapy use.

The aims of our study were to determine the prevalence of topical 5-ASA use and the effect of age, gender and race as determinants for their use in a large United States cohort of patients.

Materials and Methods

Data Sources

We performed a cross-sectional study using the Veterans Administration (VA) National Patient Care Database from fiscal years 2003-2009. The study was approved by the IRB of Baylor College of Medicine. Specifically, we used the Inpatient and Outpatient Medical SAS datasets, which contain patient-level data. The data within these datasets include demographics (age, gender, race/ethnicity), encounters (date and frequency) and diagnosis codes [International Classification of Diseases, 9th Revision, (ICD-9)]. Race/ethnicity was designated as Caucasian (non-Hispanic), Black, Hispanic, and other. The VA Decision Support Systems (DSS) database was used to obtain pharmacy utilization data of filled prescriptions, fill dates, and days of medication dispensed.

UC case definition

VA users with UC were identified using a previously validated ICD-9 diagnosis code algorithm [7] of at least two VA encounters for UC (556.x) with at least one UC-associated VA outpatient encounter from the fiscal years 2003-2009. Patients with any ICD-9 codes for Crohn's disease (555.x) were excluded. In order to evaluate only patients who received care through the VA, patients with no filled prescriptions for an IBD medication (5-ASA, prednisone, azathioprine, 6-mercaptopurine, methotrexate, infliximab, adalimumab, or certolizumab pegol) during the study period were excluded. Patients with missing information for gender or race were excluded.

Determination of 5-aminosalicylic acid therapy use

Data for filled prescriptions of 5-ASA from the VA were obtained from DSS. Oral 5-ASA therapy was classified as a filled prescription for any oral formulation of mesalamine, sulfasalazine, or balsalazide. Topical 5-ASA therapy was classified as either suppository or enema.

Statistical analysis

The crude period prevalence of 5-ASA therapy usage over the study period was determined for topical and oral 5-ASA separately. For the study period, the total number of patients with a filled prescription for topical 5-ASA therapy was used as the numerator and the total number of UC patients included in the analyses was used as the denominator. Similarly, the total number of patients with a filled prescription for oral 5-ASA therapy was used as the numerator and the total number of UC patients included in the analyses was used as the denominator.

Determinants of topical 5-ASA therapy use were identified using univariate and multivariate analysis. Variables with a p-value <0.05 were included in the multivariate logistic regression model. Among patients prescribed both formulations of topical 5-ASA therapy, the sequence and timing of transition were analyzed. Statistical analysis was performed using STATA version 13 software (College Station, TX).

Results

Prevalence of topical and oral 5-ASA therapies

A total of 26,242 patients with UC were initially identified using the ICD-9 code case finding algorithm described. Of these patients, 5,713 patients were excluded because they did not have either gender or race information; 20,259 patients were included in the analysis.

The prevalence of any filled prescription for 5-ASA (oral or topical) therapy was 81%; 77% for any oral and 27% for any topical. Among the study population, the prevalence of filled prescriptions for suppositories and enemas was 14% and 19%, respectively. (**Table 1**) shows the baseline characteristics for the groups who filled topical 5-ASA and those who did not. Of the patients who filled topical therapies, their mean age was 56 years and the majority were Caucasian (81%) men (93%).

Effects of Age, Gender and Race on use of topical 5-ASA therapies

Patients who filled topical therapies were significantly younger

Table 1 Baseline Demographics by Filled Topical 5-ASA therapy prescriptions.

	Topical 5-ASA (n=5,604)	No Topical 5-ASA (n=14,925)	P value
Age at diagnosis (yrs), mean (SD)	56 (16)	61 (14)	<0.05
Gender, n (%)			
Male	5,212 (93)	14,158 (95)	<0.05
Female	392 (7)	767 (5)	<0.05
Female	392 (7)	767 (5)	<0.05
Race			
Caucasian	4,543 (81)	13,093 (88)	<0.05
Black	647 (12)	1009 (7)	<0.05
Hispanic	286 (5)	542 (4)	<0.05
Other	128 (2)	281 (1)	<0.05

than those who did not fill prescriptions (OR 0.978, 95% CI 0.976-0.980). A univariate logistic regression analysis showed that females were more likely to fill topical 5-ASA therapies than males (OR 1.39, 95% CI 1.22-1.57). Similarly, Blacks, Hispanics and other non-Caucasian races were more likely to fill topical 5-ASA therapies compared to Caucasians (Table 2).

Age, gender and race were tested for interactions using a multivariate logistic regression model. Age (OR 0.980, 95% CI 0.978-0.982), Black race (OR 1.53, 95% CI 1.38-1.71) and Hispanic ethnicity (OR 1.33, 95% CI 1.15-1.55) remained significant variables associated with the use of topical 5-ASA therapies. However, female (OR 0.99, 95% CI 0.87-1.13) and other races (OR 1.18, 95% CI 0.95-1.46) lost their significance.

Sequence and switching among topical 5-ASA therapies

A total of 1,310 patients filled prescriptions for both suppository and enema 5-ASA formulations during the study period. Of these patients, 58.5% were initially prescribed an enema before using suppositories, 34.6% were initially prescribed suppositories before using enemas and 6.95% were provided both topical medications at the time of diagnosis. When patients were switched between medications, the majority (25-49%) switched after 90 days (Table 3). The results revealed a higher percentage of people switched from suppositories to enemas in less than 30 days (5.5%) compared to those changing from enemas to suppositories (4.81%) (p=0.45).

Discussion

We performed a national cross sectional study to determine the prevalence of topical 5-ASA use and associations between topical 5-ASA use and age, gender, and race among patients with UC. We found a low prevalence of topical 5-ASA use compared to prior studies. Despite guideline recommendations for the use of topical or combination oral and topical 5-ASA therapy in mild to moderate UC, topical therapy is rarely used. We found only 27% of UC patients had filled prescriptions for topical 5-ASA therapies. Our findings are in sharp contrast with prior studies from Europe, where 74-81% of physicians recommended treating mild to moderate ulcerative proctitis with topical 5-ASA therapy [5]. Possible reasons our observed prevalence is markedly lower than the European studies is that we analyzed filled prescriptions and included all patients with UC regardless of disease extent. Our observed prevalence is similar to other U.S. based studies, ranging from 25-53 %. [4, 8]

We observed no difference in 5-ASA use by gender, similar to that reported in prior studies. Data from the University of Manitoba IBD Database showed no gender-specific differences in oral 5-ASA therapy use and did not report the gender specific results for topical therapies [9]. Similar findings were reported from a German study exploring differences in IBD treatment. They found no significant difference in 5-ASA therapy use, but did find women were less likely to receive immunosuppressive medications (azathioprine, methotrexate, 6-mercaptopurine, cyclosporine, tacrolimus) compared to men [10].

Differences in topical 5-ASA use among patients with UC separated by race have not previously been described. We observed Blacks and Hispanics were more likely than Caucasians to use topical 5-ASA therapy. A study (184 patients) from Houston, TX reported the treatment patterns among different racial groups (40% Caucasian, 37% Black, 20% Hispanic and 3% Asian). They found no significant difference in use of 5-ASA therapies, but topical therapies were not specifically examined [11]. Sewell et al. performed a retrospective study of patients from San Francisco General Hospital and found any 5-ASA use was less common among Blacks and Hispanics [12]. They, however, did not separately analyze oral and topical 5-ASA therapies. These differences may be explained by our focus on topical therapies, compared to those studies analyzing overall 5-ASA therapy use. Another potential reason for differences in topical 5-ASA use by race is differences in UC extent. Blacks (17-23%) and Hispanics (4-56%) have a higher proportion of proctitis compared to non-

Table 2 Univariate and Multivariate Logistic Regression Analysis for Age, Gender and Race as Determinants of Topical 5-ASA therapy use.

	Univariate		Multivariate	
	OR	95% CI	OR	95% CI
Age	0.978	0.976-0.980	0.98	0.978-0.982
Gender				
Male	Ref	-	Ref	-
Female	1.39	1.22-1.57	0.99	0.86-1.13
Race				
Caucasian	Ref	-	Ref	-
Black	1.85	1.66-2.05	1.53	1.38-1.71
Hispanic	1.52	1.31-1.76	1.33	1.15-1.55
Other	1.31	1.06-1.62	1.18	0.95-1.46

Table3 Frequency of Changing Topical 5-ASA among Patients Prescribed both Formulations.

	Suppositories to Enemas, n=453(%)	Enemas to Suppositories, n=766 (%)	P value
<30 days	72 (5.50%)	63 (4.81%)	0.60
30-60 days	38 (2.90%)	34 (2.60%)	0.76
60-90 days	21 (1.60%)	22 (1.68%)	0.92
>90 days	322 (24.58%)	647 (49.39%)	<0.05

Hispanic Caucasians (6-10%) [11, 13-15]. Based on this, we would assume Blacks and Hispanics should receive topical 5-ASA therapies more often than Caucasians, which is in agreement with our findings.

Almost of quarter of patients prescribed topical 5-ASA had filled prescriptions for both enema and suppository 5-ASA formulations throughout our study period. We observed nearly twice as many patients were switched from enemas to suppositories compared to switching from suppositories to enemas. We hypothesize this change in usage pattern of topical 5-ASA therapy is related to improved tolerance of suppositories compared to enemas; however, further studies considering disease extent are needed to confirm this observation.

Our study has several strengths, most notably the large sample size and accuracy of VA national pharmacy databases and use of filled prescriptions rather than prescribed medications or physician self-report. Furthermore, VA care centers are community based and less likely to have referral bias frequently seen in data from tertiary care centers. Limitations of our study include inherent limitations from utilizing administrative data. The VA population is predominantly male; therefore, we may have been underpowered to assess gender differences. Additionally, we included all patients treated through the VA system, without distinguishing incident and prevalent cases, therefore prevalent cases may have received topical therapies prior to seeking treatment at the VA. Regarding definitions for disease extent, ICD-9 codes accounting for disease extent exist, but they are inaccurate [16]. Further studies accurately accounting for disease extent will be needed.

In conclusion, prevalence of topical 5-ASA therapy use is low. Black and Hispanic patients are more likely to receive filled prescriptions of 5-ASA compared to non-Hispanic Caucasians. Further studies are needed to explore confounding factors, such as disease extent, and potential differences in outcomes related to topical 5-ASA therapy use.

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