

5-ASA to Sulfasalazine Drug Switch Program in Patients With Ulcerative Colitis

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Approximately 800,000 patients in the United States live with ulcerative colitis (UC),¹ an inflammatory condition of the large intestine. Patients with UC experience extensive morbidity, including abdominal pain, diarrhea, weight loss, and fever. Chronic inflammation can lead to colon cancer, whereas other complications often necessitate bowel resection; additionally, severe extraintestinal manifestations exist.^{2,3} Sulfasalazine and 5-aminosalicylic acid (5-ASA) agents are effective medications for the induction of remission and maintenance in mild to moderate UC.⁴ These oral medications are cost-effective therapy for UC, and regular use of these agents can greatly reduce the costs of UC to patients, payers, and society.⁵ Additionally, the current literature suggests a chemoprotective effect of 5-ASAs, helping to tamp down the increased risk of colorectal cancer seen in patients with UC,⁶⁻⁸ providing further long-term positive outcomes and cost benefits.⁸ Sulfasalazine is a very effective, low-cost therapy for UC, with a 72% success rate for induction and maintenance of remission in patients with UC.^{9,10} Unfortunately, sulfasalazine has lost popularity in the gastrointestinal community because up to 30% of patients experience an adverse event (AE).¹¹ Nausea, headaches, and fever are the most common reactions; thus, newer 5-ASA products that lack the sulfa moiety unique to sulfasalazine, and with fewer AEs, have been developed, but these have substantially greater costs. Sulfasalazine has the longest track record, has similar or better efficacy than its derivative 5-ASAs,^{4,12,13} and is the cheapest of all available formulations. Furthermore, some of the AEs associated with it may be avoided through slow upward titration to a limiting dose, but this requires active management by clinical staff and so is often not attempted before switching to a 5-ASA.

We thus attempted such an active management approach to achieve cost savings while maintaining clinical efficacy. In this study, we undertook a medication switch program for all patients cared for by the University of Michigan Health System (UMHS)'s Ulcerative Colitis Clinic who were on 5-ASA products for their UC and were enrolled in a health plan participating in this program, in order to help decrease the medication cost burden to both the patients and payers.

ABSTRACT

OBJECTIVES: To switch patients with ulcerative colitis (UC) from costlier 5-aminosalicylic acid compounds to sulfasalazine and assess (1) the cost savings, (2) the barriers to switching, and (3) adverse events (AEs) and adherence at 3 months after the drug switch.

STUDY DESIGN: An open-label, pharmacist-administered drug switch program coordinated at an academic inflammatory bowel disease center.

METHODS: A clinical pharmacist contacted patients with UC who were prescreened by physicians and covered by specific insurers to enroll them in the drug switch program. Enrolled patients were followed for 3 months to assess AEs and medication adherence. Reasons for declining to participate were recorded.

RESULTS: A total of 205 eligible patients were identified; only 14 enrolled, and 10 remained on sulfasalazine for the entire 3-month follow-up period. The enrollment rate was only 4.9%, yet a net cost savings of \$22,828/3-month to the insurer was achieved (including program administration costs but excluding AE costs), with co-pays reduced by approximately \$25 per month per patient. The rate of AEs on sulfasalazine (28.6%) was similar to that found in previous reports. Significant unanticipated barriers to switching were encountered, namely patient desire to not alter an existing effective drug regimen.

CONCLUSIONS: A pharmacist-administered drug switch program in patients with UC was significantly more difficult than anticipated, with questionable achievement of cost savings. This experience suggests that future drug switches and studies should focus on patient preferences for drug switching, as this may have implications for switching from brand name to biosimilar drugs.

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TAKEAWAY POINTS

A 5-aminosalicylic acid to sulfasalazine drug switch program was instituted for patients with ulcerative colitis. Major unanticipated barriers limited the number of patients who switched, but significant savings were still achieved.

- ▶ Although only 4.9% of eligible patients successfully switched (n = 10), the annualized net cost savings was \$91,313.
- ▶ The greatest barrier to switching was a desire among patients to “not rock the boat,” which appears to be unique to drug switch programs involving active chronic disease.
- ▶ This barrier could impede switching of patients from brand name biologics to new, cheaper biosimilars. Patient financial incentives were minimal in our program and could be amplified for biosimilars.

METHODS

Program Overview

This program was implemented at UMHS, a nonprofit teaching institution that provides more than 2.3 million outpatient visits annually at 3 hospitals and 30 health centers, including 120 primary care or specialty clinics. It serves a large multipayer population. The program was developed in a similar fashion to a previous switch program by UMHS that involved the use of generic simvastatin from branded atorvastatin (Lipitor).¹⁴

Patients received a letter informing them of a cost-saving opportunity by switching from a 5-ASA to sulfasalazine. Gastroenterologists received an introductory email about the switch program, reasons

for the switch, and how it would be conducted. In addition, presentations about the program were given to the gastroenterologists at their divisional meetings and the inflammatory bowel disease work group meetings.

Patient Selection

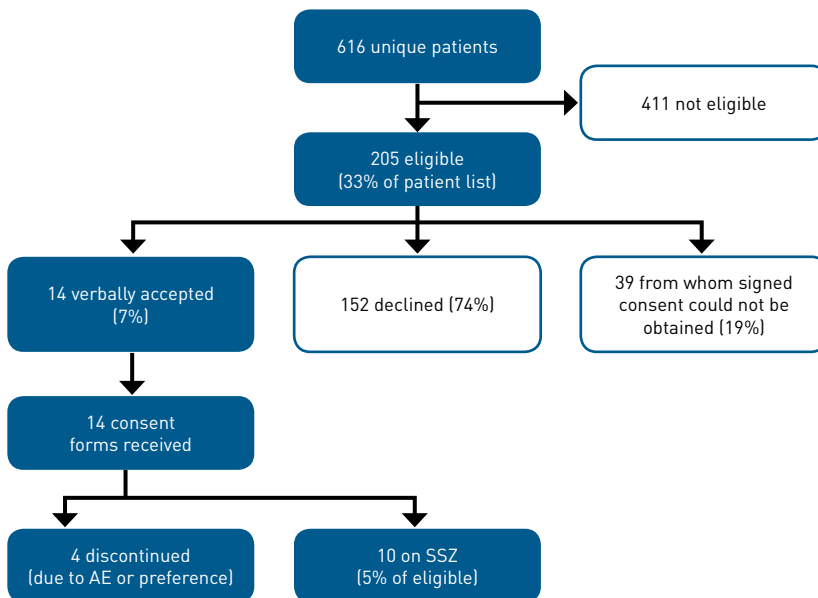
Eligible patients were identified from electronic health records (EHRs). Patients were identified as eligible if, as of October 2014, they (1) had a diagnosis of UC, (2) were on a 5-ASA other than sulfasalazine at stable dosages, (3) were receiving care from a UMHS gastroenterologist, (4) were approved for the switch by their gastroenterologist, and (5) were insured by Blue Cross Blue Shield of Michigan or Blue Care Network. Patients who had a sulfa allergy or intolerance were excluded from the switch program. This trial was presented at the monthly UC clinic physician meeting, and preapproval for the drug switch by the patient’s gastroenterologist was obtained through secure email by the clinical research coordinator or clinical pharmacist before the patient was contacted by phone (contact via the aforementioned mailings occurred prior to physician approval). The presentation was generally well received. The objections to enrollment from the gastroenterologists were for patients who (1) recently had their disease become well controlled, (2) had a history of unstable disease, or (3) had an undocumented history of failed sulfasalazine therapy. The **Figure** outlines this process.

Program Design

The clinical research coordinator created an electronic database that included fields for (1) patient demographics (eg, name, age, sex, address, phone), select medication history, simple clinical colitis activity index (SCCAI) score,¹⁵ and most recent laboratory values (erythrocyte sedimentation rate, C-reactive protein, comprehensive metabolic panel, complete blood counts, and fecal calprotectin) from our health system’s electronic data warehouses; (2) responses from the introductory script and questionnaire (**eAppendix A** [eAppendices available at ajmc.com]); and (3) fields for the data to be collected throughout the study, as described below.

Using a standardized script approved by UMHS’ institutional review board (IRB) (**eAppendix A**), the clinical pharmacist informed patients about the program, explained that their physicians had approved the switch, and

FIGURE. Enrollment Algorithm^a



AE indicates adverse event; SSZ, sulfasalazine.

^aA total of 616 unique patients were identified in the University of Michigan Health System’s Ulcerative Colitis Clinic. Of these, 205 were eligible; 152 patients declined and consent was not obtained for 39 patients, leaving 14 patients to enroll. Of the 14 enrolled, 4 discontinued due to AEs or preference and 10 continued on SSZ.

asked them whether they wanted to switch from their current 5-ASA to sulfasalazine. If a patient was not interested in switching, the pharmacist documented why they were uninterested in switching. If patients were not reached, a voicemail was left following an IRB-approved script (eAppendix B). A maximum of 6 attempts were made to contact each patient, including morning and afternoon phone calls. An information sheet was mailed to patients who could not be contacted. Patients who elected to switch received new prescriptions for sulfasalazine titration (500 mg once daily for 3 days; then 500 mg twice daily for 3 days; then 1000 mg in the morning and 500 mg in the evening for 3 days; then 1000 mg twice daily) and folic acid (1 mg once daily), which were sent to their preferred pharmacy within 24 hours. Each patient also received a letter confirming the medication change. Two weeks after the medication change, patients were contacted for follow-up SCCAI score, steroid prescription use, and hospital or provider visits for UC activity. If SCCAI score was less than 4, patients were continued on therapy and follow-up laboratory tests were electronically entered for draw 4 to 6 weeks later. These laboratory tests included a comprehensive metabolic test (serum levels of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase), complete blood count, erythrocyte sedimentation rate, C-reactive protein, and fecal calprotectin. If SCCAI score was 4 or higher, the sulfasalazine dose was further escalated as follows: 1500 mg in the morning and 1000 mg in the evening for 3 days; 1500 mg twice daily for 3 days; 2000 mg in the morning and 1500 mg in the evening for 3 days; then 2000 mg twice daily for 3 days. Additional follow-up occurred 2 weeks afterwards, including a new SCCAI score and assessment of steroid prescription use and hospital or provider visits for UC activity. In the additional follow-up, if the SCCAI score was less than 4, patients were continued on therapy and follow-up laboratory tests were electronically entered for draw 4 to 6 weeks later. If SCCAI score was 4 or higher, patients were routed to a gastroenterologist for determination of further sulfasalazine dose escalation or switching to alternative therapy. The patients' EHRs were updated to reflect the change in medication and a note was entered into the medical chart for each patient encounter.

Outcome Measures

All patients contacted for the study were assessed for their willingness to switch to sulfasalazine. All patients enrolled in the study were followed for a period of 3 months after enrollment. We measured and reported the following end points: (1) rate of willingness to switch to sulfasalazine; (2) rate of success of switch to sulfasalazine (in those who attempted), defined as those patients still on sulfasalazine at the end of the 3-month study period; (3) total and per patient and per payer cost savings over the course of the 3-month period, compared with prior year costs; and (4) patient outcome measures, including

TABLE 1. Causes of Ineligibility Among Potential Study Participants^a

Ineligibility Cause	Number of Subjects (%)
Not on 5-ASA	138 (33.6)
Sulfa allergy/intolerance	95 (23.1)
Not approved by gastroenterologist	86 (20.9)
Not currently under the care of a UMHS gastroenterologist	83 (20.2)
Already on SSZ	16 (3.9)
Other ^b	13 (3.2)
Does not have definitive UC	12 (2.9)

5-ASA indicates 5-aminosalicylic acid; SSZ, sulfasalazine; UC, ulcerative colitis; UMHS, University of Michigan Health System.

^aTotals add up to more than 100%, as patients could have been ineligible for more than 1 reason.

^bIncludes reasons such as being part of the study research staff, pregnancy, and current hospitalization.

disease exacerbations defined as emergency department (ED) visits, hospitalizations, and discontinuing sulfasalazine.

Data Analysis

Demographic variables were compared using the independent *t* test for continuous variables; χ^2 and Fisher exact tests were used to compare categorical variables. A 2-tailed *P* value <.05 denoted the statistical significance. The statistical analyses were performed using R Statistical Software (R 3.3.2).

RESULTS

At the UMHS UC clinic, 616 patients were identified. Of these, 411 were not eligible. Most were ineligible due to the patient not being on a 5-ASA product or having a sulfa allergy or intolerance, but a significant number were also disqualified due to lack of physician approval (20.9%) or because they were currently not receiving care from a UMHS physician (20.2%) (Table 1). For a few patients (2.9%), their diagnosis of UC (vs indeterminate colitis or Crohn colitis) was not definitive, and they were also excluded. Of the 205 eligible patients (33.3% of the total pool), only 14 were enrolled and completed the consent process (Figure), whereas the majority (152 patients) declined to participate (Figure) and for 39 patients a signed consent could not be obtained (Figure). Demographic analysis of the accepting versus declining patients showed no significant differences, although patients who accepted had a trend toward longer mean disease duration (16.36 vs 12.32 years; *P* = .091; Table 2). Of the 14 patients who were successfully enrolled, 4 (28.6%) switched off sulfasalazine due to AEs (3 patients) or patient preference (1 patient), which is in line with previous reports.¹¹ Because the number of enrolled patients in this study was so low, we could not determine if pharmacist guidance was able to decrease discontinuation rates compared

ORIGINAL RESEARCH

TABLE 2. Demographics of Eligible Patients by Enrollment Status

Characteristic	Accepted (n = 14)	Declined (n = 152)	P
Gender (female), %	42.86	51.32	.744
Age, years, mean (SD)	54.36 (15.48)	51.20 (15.40)	.464
Race, %			.169
White	78.6	90.1	
Black	7.1	2.6	
Asian	7.1	5.9	
Unknown	7.1	1.3	
Disease duration, years, mean (SD)	16.36 (8.78)	12.32 (8.49)	.091
Extent of disease, %			.598
Proctitis	7.1	3.8	
Left-sided	14.3	27.0	
Extensive	0.0	2.0	
Pancolitis	78.6	51.3	
Unknown	0.0	5.9	
Duration on 5-ASA, years, mean (SD)	3.83 (1.48)	3.76 (1.44)	.862

5-ASA indicates 5-aminosalicylic acid.

with previous studies without pharmacist guidance.¹¹ Furthermore, this low number of participants prevented our intended analysis of predictors of patient outcomes.

Cost Savings

The monthly cost savings for the insurer for the 10 patients who successfully switched and remained on sulfasalazine for the 3-month follow-up were \$9056 (Table 3). The hourly wage and benefits for

an outpatient care center pharmacist, who administers such a plan, is approximately \$77.50 per hour.¹⁶ The total time spent by our pharmacist, including working up the 205 eligible patients, communicating with physicians, direct patient contact, clinic note documentation, and patient follow-up, but excluding time spent exclusively on research-specific tasks, was 56 hours, equal to \$4340. Taking the monthly cost savings, multiplying it by 3, and then subtracting the time spent by our pharmacist yielded a net cost savings of \$22,828 for the 3-month follow-up period from these 10 enrolled patients (4.9% of the total pool).

Analysis of Patient Decline Rationale

As previously mentioned, a surprisingly large number of patients declined to switch. In our previous statin-switching study, we had a decline rate of 41% of eligible patients,¹⁴ compared with a rate of 74% in this study (Figure). Of the patients who declined, the dominant reason (patients could list more than 1 reason) was a generic unwillingness to switch (59.9%), which was often articulated to our pharmacist as a “don’t fix what isn’t broken” resistance to changing medication, or specific fear of a flare (10.5%) (Table 4). Other concerns, which were more anticipated, included: minimal personal financial gain for the effort to switch (18.4%), concerns about AEs (16.4%), the time involved to complete the switch process (11.1%), a bad prior (undocumented) experience with sulfasalazine (7.2%), competing life events that precluded time to initiate a switch (4.6%), and a desire to avoid being part of a research program (3.3%) (Table 4). This large portion of patients who “didn’t want to mess with success” demonstrates a significant barrier that was present in patients with UC but was relatively absent in patients on maintenance medications for more “silent” diseases (such as cardiovascular disease/risk management with our statin-switching program¹⁴). This barrier could not be

TABLE 3. Cost Savings to Insurers Generated by Switching 10 Patients From a 5-ASA to Sulfasalazine*

Patient #	5-ASA Tabs/Month	5-ASA Cost/Tab	5-ASA Cost/Month	SSZ Daily Dose	SSZ Cost/Tab	SSZ Cost/Month	Insurance Cost Savings/Month
1	120	\$4.42	\$530.40	120	\$0.32	\$38.40	\$492.00
2	180	\$6.40	\$1152.00	120	\$0.32	\$38.40	\$1113.60
3	180	\$6.40	\$1152.00	120	\$0.32	\$38.40	\$1113.60
4	90	\$10.31	\$927.90	120	\$0.32	\$38.40	\$889.50
5	180	\$6.40	\$1152.00	120	\$0.32	\$38.40	\$1113.60
6	180	\$3.88	\$698.40	120	\$0.32	\$38.40	\$660.00
7	60	\$10.31	\$618.60	120	\$0.32	\$38.40	\$580.20
8	360	\$3.88	\$1396.80	240	\$0.32	\$76.80	\$1320.00
9	180	\$6.40	\$1152.00	120	\$0.32	\$38.40	\$1113.60
10	180	\$3.88	\$698.40	120	\$0.32	\$38.40	\$660.00
TOTAL							\$9056.10

5-ASA indicates 5-aminosalicylic acid; SSZ, sulfasalazine.

*Costs were obtained from specific patient formularies. Variations in the 5-ASA price per tablet were due to cost differences among the different 5-ASAs that patients were on before the switch.

overcome by the relatively small personal benefit they would see in terms of co-pay reduction (\$25/month on average among the 7 patients who switched whose co-pay information could be obtained, of the 10 total patients who switched). Of note, being involved in a research study was not a significant barrier in our study.

DISCUSSION

Many medication prescription practices today do not take into account the significant financial burdens to both patients and insurers that are incurred with a given prescription. One such example of this is with sulfasalazine, a low-cost generic anti-inflammatory for UC (and Crohn disease) that has been largely replaced by 5-ASA compounds due to their smaller AE profile and fewer number of pills required per day. However, these 5-ASA compounds are significantly more expensive, and the AEs of sulfasalazine are not universally experienced.¹¹ However, it is more convenient for both the physician and the patient if these events can be completely avoided, and so sulfasalazine has fallen by the wayside despite its equal or superior efficacy.^{4,12,13}

We attempted to overcome this prescribing practice by engaging in a pharmacist-directed drug switch program. Of 205 eligible patients, only 10 were successfully switched to sulfasalazine for at least 3 months. This resulted in a net cost savings of \$22,828 for the 3-month follow-up period for the insurer. Patients saved approximately \$25 per month on average, which, although a much smaller amount, is still a meaningful benefit for the patients who switched. It should be noted, however, that these cost calculations are limited in that they do not include costs from any AEs from switching, such as hospitalization or ED visits, which could consume all of the savings achieved. Additional lab costs, however, were particular to the research study and would not generally exist in a standard switch program, as they would occur as part of existing patient care.

However, in the course of this drug switch study, we encountered significant resistance to switching, as 74% of patients declined to switch, as opposed to 41% who declined in a similar statin-switching program.¹⁴ This large population of patients who declined was initially unanticipated and demonstrated significant psychosocial barriers to switching. The majority of patients declined out of a desire to “not fix what isn’t broken,” an attitude that seems unique to patients with chronic diseases that require constant medical therapy to keep their symptoms in check. This is of particular concern given the rise of biosimilars for more potent and costly biologic UC drugs, such as infliximab.¹⁷ The cost savings from switching from infliximab to an equivalent biosimilar are significant, anticipated to reach as much as \$112 billion over the next 5 years in the United States,¹⁸ and so insurer-mandated switching of patients from brand name biologics to equivalent biosimilars has already started, especially in European countries where health insurance is publicly funded.¹⁸ Given the psychosocial barriers that we encountered with 5-ASAs,

TABLE 4. Study Decline Reasons^a

Study Decline Reasons	Subjects, n (%)
Wants to remain on current medication	91 (59.9)
Other ^b	31 (20.3)
Cost benefit not enough	28 (18.4)
Concerned about adverse events	25 (16.4)
Medication multiple times per day	23 (15.1)
Time	17 (11.1)
Afraid of flare	16 (10.5)
Previously took SSZ and does not want to again	11 (7.2)
Competing life events	7 (4.6)
Does not want to participate in research	5 (3.3)
Wants to talk to doctor	4 (2.6)

SSZ indicates sulfasalazine.

^aTotals add up to more than 100%, as many patients had more than 1 reason to decline.

^bOther includes reasons such as unwillingness to take folic acid supplement, number of SSZ pills that need to be taken, and cost of laboratory tests.

which are the lowest-intensity drug class for UC treatment, we can only anticipate that these barriers will be magnified when drug-switching strategies are applied to the higher-potency biologics. This will likely result in significant patient resistance to such programs and possible political backlash in countries where healthcare is publicly insured. One possible way to overcome this barrier would be to provide direct financial incentives (beyond plan-based co-pay reductions) to those patients who switch, which our study did not do; a lack of financial incentives was a reason to decline enrollment in 18.4% of our patients.

Limitations

Given that we were only able to enroll 14 eligible patients, the outcomes data of patients who switched to sulfasalazine were severely limited. Other limitations in this study include minimal information regarding the eligible patients from whom we were unable to obtain consent (n = 39). Consent could not be obtained for a variety of reasons, including an inability to reach the patient or failure to complete the written consent. The underlying reasons for these failures remain unknown and could have been due to our explored reasons for declining participation or other factors.

CONCLUSIONS

In conclusion, this 5-ASA drug switch program in patients with UC revealed significant and unanticipated resistance to drug switching within a relatively low-potency UC drug class. This should serve as a warning for upcoming drug switch programs for biologic therapies that are of much higher potency and much more expensive, and proper incentivization should be included in such programs to overcome the barriers we encountered here. With the low switch

rate we encountered, the large per patient savings achieved through switching were likely offset by the additional costs from AEs. Going forward, future drug switch programs should consider patient barriers before implementation, especially in patients with active chronic illness. ■

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REFERENCES

- Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology*. 2004;126(6):1504-1517. doi: 10.1053/j.gastro.2004.01.063.
- Barrie A, Plevy S. Treatment of immune-mediated extraintestinal manifestations of inflammatory bowel disease with infliximab. *Gastroenterol Clin North Am*. 2006;35(4):883-893. doi: 10.1016/j.gtc.2006.09.001.
- Sandborn WJ. Current directions in IBD therapy: what goals are feasible with biological modifiers? *Gastroenterology*. 2008;135(5):1442-1447. doi: 10.1053/j.gastro.2008.09.053.
- Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2003;(3):CD000543. doi: 10.1002/14651858.CD000543.
- Yen EF, Kane SV, Ladabaum U. Cost-effectiveness of 5-aminosalicylic acid therapy for maintenance of remission in ulcerative colitis. *Am J Gastroenterol*. 2008;103(12):3094-3105. doi: 10.1111/j.1572-0241.2008.02130.x.
- Margagnoni G, Pagnini C, Menasci F, Festa S, Delle Fave G. Critical review of the evidence on 5-aminosalicylate for chemoprevention of colorectal cancer in ulcerative colitis: a methodological question. *Curr Clin Pharmacol*. 2014;9(1):84-90. doi: 10.2174/157488470866613111202337.
- Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. *Am J Gastroenterol*. 2005;100(6):1345-1353. doi: 10.1111/j.1572-0241.2005.41442.x.
- Rubenstein JH, Waljee AK, Jeter JM, Velayos FS, Ladabaum U, Higgins PD. Cost effectiveness of ulcerative colitis surveillance in the setting of 5-aminosalicylates. *Am J Gastroenterol*. 2009;104(9):2222-2232. doi: 10.1038/ajg.2009.264.
- Sutherland L, Roth D, Beck P, May G, Makiyama K. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2002;(4):CD000544. doi: 10.1002/14651858.CD000544.
- Saini SD, Waljee AK, Higgins PD. Cost utility of inflammation-targeted therapy for patients with ulcerative colitis. *Clin Gastroenterol Hepatol*. 2012;10(10):1143-1151. doi: 10.1016/j.cgh.2012.05.003.
- Nielsen DH. Sulfasalazine intolerance: a retrospective survey of the reasons for discontinuing treatment with sulfasalazine in patients with chronic inflammatory bowel disease. *Scand J Gastroenterol*. 1982;17(3):389-393.
- Sutherland LR, May GR, Shaffer EA. Sulfasalazine revisited: a meta-analysis of 5-aminosalicylic acid in the treatment of ulcerative colitis. *Ann Intern Med*. 1993;118(7):540-549. doi: 10.7326/0003-4819-118-7-199304010-00009.
- Hanauer SB. Review article: high-dose aminosalicylates to induce and maintain remissions in ulcerative colitis. *Aliment Pharmacol Ther*. 2006;24(suppl 3):37-40. doi: 10.1111/j.1365-2036.2006.03058.x.
- Sy FZ, Choe HM, Kennedy DM, et al. Moving from A to Z: successful implementation of a statin switch program by a large physician group. *Am J Manag Care*. 2009;15(4):233-240.
- Walmstey RS, Ayres RCS, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut*. 1998;43(1):29-32. doi: 10.1136/gut.43.1.29.
- Occupational employment and wages, May 2017: 29-1051 pharmacists. Bureau of Labor Statistics website. [bls.gov/oes/current/oes291051.htm](https://www.bls.gov/oes/current/oes291051.htm). Accessed March 1, 2017.
- Martelli L, Peyrin-Biroulet L. Efficacy, safety and immunogenicity of biosimilars in inflammatory bowel diseases: a systematic review [published online October 14, 2016]. *Curr Med Chem*. doi: 10.2174/0929867323666161014153346.
- Danese S, Bonovas S, Peyrin-Biroulet L. Biosimilars in IBD: from theory to practice. *Nat Rev Gastroenterol Hepatol*. 2017;14(1):22-31. doi: 10.1038/nrgastro.2016.155.

Full text and PDF at www.ajmc.com

eAppendix A

Introductory script and survey

Hello, this is [interviewer] from University of Michigan Health Care System. May I please speak with [patient]?

Hello, [patient], my name is [interviewer] from the University of Michigan Health Care System. I am contacting you in regard to one of the medications you are taking for your ulcerative colitis, specifically [specific 5-ASA]. We are starting a drug switch program, where we are working to switch patients from more expensive 5-ASAs, like [specific 5-ASA], to sulfasalazine, which is a generic medication and will cost less for you (you will have a lower copay), and your insurance company. Your physician, Dr. [patient's physician] has identified you as a good candidate for this switch, and he/she has pre-approved the switch, if you approve to this switch.

Before explaining the switch program, I would like to ask you a few questions regarding your ulcerative colitis. Is that okay?

1) Our records indicate that your inflammatory bowel disease involves your colon - is that correct?

2) Our records indicate that you are X years old – is that correct?

3) Our records indicate that you are [gender] – is that correct?

4) Our records say you do not have a sulfa allergy – is that correct?

5) Did you know that sulfasalazine was a cheaper alternative than [specific 5-ASA] you are on? Specifically, it costs [insurance-specific sulfasalazine cost information] compared to [insurance-specific 5-ASA cost information].

6) [If no to #5, ask #6; if yes, skip] Would you have like to have known earlier that sulfasalazine was a cheaper alternative?

7) Who would you want to provide this information: Physician, Insurance Company, Pharmacist, Other? (Specify if other)

Thank you for your time answering these questions. While sulfasalazine is just as or possibly more effective than other medicines for ulcerative colitis, there is an increased risk of side effects, particularly nausea and headaches, compared to the newer drugs. Thus, part of this switch program is a clinical trial where we would observe your medical records over the course of 3 months to see how you are doing, as well as get an initial set of labs like what your doctor already gets for you, before starting the medication. Would you be interested in this study?

[If yes, informed consent text and verbal consent, to be created in conjunction with the University of Michigan Health System Institutional Review Board (IRB).]

In order to complete the drug switch, there are only a few more things we need to go over.

First, it appears that you prefer to use pharmacy X – is that correct? [confirm information].

Thank you, we will place a new prescription for sulfasalazine plus folic acid at the pharmacy.

Once you receive your prescription, you can switch. Please stop taking [specific 5-ASA] and start taking sulfasalazine. You will take two 500 mg tabs twice a day, plus a folic acid pill once a day. To minimize side effects, we will continue to titrate up sulfasalazine, adding 1 tablet (500 mg) per day every 3 days until SCCAI <4 achieved or maximum dose of 2 g twice a day is reached for a daily maximum dose of 4 g. Do you have any questions about this dosing? [answer questions]

Secondly, as we mentioned you will need to have some labs done in the next 4-6 weeks. We will place the orders for the labs into MIChart, so all you will need to do is come to a U of M lab for a blood draw sometime in the next 4-6 weeks. The cost of the labs will be covered in the same fashion as they normally are by your insurance. Will that be possible? Do you have any questions? [answer questions]

Are there any other questions I can answer for you?

Thank you for your time.

eAppendix B

“Hello, I’m calling for Mr/Mrs [last name]. I am a pharmacist from the University of Michigan working with Dr. [gastroenterologist last name]. We would appreciate it if you could return my call [pharmacist phone number] at your earliest convenience. Thank you and have a good day.”