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No Benefit of Continuing 5-Aminosalicylates in Patients with Crohn's disease Treated with Anti-metabolite Therapy

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Abstract

BACKGROUND and AIMS: 5-aminosalicylates (5-ASA) are frequently used in the management of Crohn's disease (CD). We used a de-identified administrative claims database to compare patterns and outcomes of continuing versus stopping 5-ASA in patients with CD who escalated to anti-metabolite monotherapy.

METHODS: Patients with CD on 5-ASA who were new users of anti-metabolite monotherapy and followed for at least 12 months from OptumLabs® Data Warehouse. Three patterns of 5-ASA use were identified: stopped 5-ASA, short-term 5-ASA (use for <6 months after starting anti-metabolites), or persistent 5-ASA (use for >6 months after starting anti-metabolites). Outcomes (need for corticosteroids, risk of CD-related hospitalization and/or surgery, treatment escalation to biologic therapy) were compared using Cox proportional hazard analysis adjusting for key covariates, with a 12-month immortal time period.

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Author Contribution

- Study concept and design: SS
- Acquisition of data: SS, JK, WZ
- Analysis and interpretation of data: DP, JK, WZ, SS
- Drafting of the manuscript: DP, SS
- Critical revision of the manuscript for important intellectual content: JK, WZ, WJS, VJ
- Approval of the final manuscript: DP, JK, WZ, PSD, WJS, VJ, SS
- Guarantor of Article: SS

RESULTS: Of 3036 patients with CD who were new-users of anti-metabolite monotherapy, 667 (21.9%), 626 (20.6%) and 1743 (57.4%) stopped 5-ASA, used 5-ASA transiently or persistently, respectively. Compared to patients who stopped 5-ASA after starting anti-metabolites, persistent 5-ASA use was associated with a higher risk of corticosteroid use (HR,1.24 [1.08–1.42]), without an increase in risk of CD-related hospitalization (HR,1.21 [0.98–1.49]), CD-related surgery (HR, 1.28 [0.90–1.80]) or treatment escalation (HR, 0.85 [0.62–1.20]). Sensitivity analyses using a 3-month window after initiation of anti-metabolites to classify patients as continuing vs. stopping 5-ASA showed similar results. Residual confounding by disease severity could not be excluded.

CONCLUSION: 5-ASAs are frequently continued long-term even after escalation to anti-metabolite therapy in patients with CD but offer no clinical benefit over stopping 5-ASA.

Keywords

Inflammatory bowel diseases; mesalamine; low value care; immunosuppressive

INTRODUCTION

5-aminosalicylates (5-ASA) are frequently used in the management of Crohn's disease (CD), though they are not recommended for induction or maintenance of remission in clinical guidelines.[1–7] Besides primary use, they are frequently continued even after escalating to immunosuppressive therapy for moderate to severe CD. In a systematic review of 44 trials of induction therapy and 10 trials of maintenance therapy with immunosuppressive agents for CD, 44% and 49% of patients were concomitantly treated with 5-ASA.[2] It remains unclear if the continuation of 5-ASA would augment the effectiveness of anti-metabolites in patients with CD. Simultaneous use of 5-ASA with thiopurines has been correlated with higher levels of 6-thioguanine (6-TGN), which could alter the efficacy of thiopurines.[8, 9] However, prior studies of patients with ulcerative colitis (UC) have failed to demonstrate a benefit of continuing 5-ASA in patients who escalated to anti-metabolite therapy.[10] Furthermore, potential chemopreventive effects of long-term 5-ASA are unclear.

There is significant attention towards reducing healthcare costs associated with inflammatory bowel diseases (IBD). The 'Choosing Wisely' campaign focuses on identifying and eliminating sources of low value care.[11, 12] While 5-ASAs may be low-cost compared to biologic therapies, their collective use, without evidence of clinical benefit, is projected to have a substantial financial burden to patients and payers. A micro-costing study forecasted that continuation of 5-ASA in immunosuppressive-treated patients with CD could result in the direct annual treatment cost of concomitant ~ $32 million for the Canadian CD population, assuming conservative estimates of CD prevalence, 5-ASA use and dose, and the lowest cost formulation.[2] While 5-ASA drugs are regularly viewed as safe, serious adverse events such as interstitial nephritis, pancreatitis, serious skin reactions, hepatitis, and blood dyscrasias can occur; furthermore, the increased pill burden when continuing 5-ASA with drug escalation could lead to lack of compliance with appropriate CD-directed therapy.[13] In addition, continued use of potentially ineffective treatments may lead to delays in escalation to more effective treatments. Therefore, continuation of 5-ASA in patients

with moderate to severe CD who have failed therapy and escalated to anti-metabolite agents likely characterizes low value care.

Using a large de-identified administrative claims database (OptumLabs® Data Warehouse), we conducted a retrospective cohort study to evaluate patterns of 5-ASA use (stopping 5-ASA vs. short-term 5-ASA use for <6m vs. persistent 5-ASA use for >6m) in patients with CD after escalation to anti-metabolite monotherapy, and compared the risk of clinically important complications based on patterns of 5-ASA use. We hypothesized that persistent use of 5-ASA in patients who escalated to anti-metabolite therapy will not be more effective than stopping 5-ASA.

METHODS

Data Source

We conducted a retrospective analysis of de-identified medical and pharmacy administrative claims from a large database, OptumLabs Data Warehouse, which included commercially insured and Medicare Advantage enrollees throughout the United States. The database contains longitudinal health information on enrollees and patients, representing a diverse mixture of ages, ethnicities and geographical regions across the United States. Medical claims included International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-9-CM; ICD-10- CM) diagnosis codes; ICD-9 and ICD-10 procedure codes; Current Procedural Terminology, Fourth Edition (CPT-4) procedure codes; Healthcare Common Procedure Coding System (HCPCS) procedure codes; site of service codes; and provider specialty codes. All study data was accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996, and because this study involved analysis of preexisting de-identified data, it was exempted from institutional review board approval.

Study Population

Between January 1, 2005 to June 30, 2018, we identified adult patients (≥18 years) with: (a) at least two ICD-9 (556.x) or ICD-10 (K51) diagnosis codes of CD, either from an inpatient or outpatient visit, (b) continuous health care enrollment with pharmacy benefits, with no anti-metabolite and biologic therapy prescription in the 12 months prior to index date (date of initiation of anti-metabolite agent; new user design), and at least a 12-month minimum enrollment in health care after index date; patients who received anti-metabolites for <12m, but still retained health care were included and considered treatment failures. We excluded patients with a simultaneous diagnosis of rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis within the previous 12 months of anti-metabolite prescription date, and patients who escalated to biologic therapy with or without anti-metabolite therapy. In the event a patient received a diagnostic code for both CD and UC, the patient was classified as having CD if the majority of diagnostic codes were for CD.

From this cohort, patients who received 5-ASA within 90 days prior to the index date were identified and subsequently used to create the study cohort of 5-ASA-treated patients who

escalated to anti-metabolite monotherapy after failure of 5-ASA. eFigure 1 outlines the study scheme.

Exposure

The exposure pattern of oral 5-ASA after introduction of anti-metabolite monotherapy (index date) was categorized as: stopping 5-ASA (no additional prescription of 5-ASA, including sulfasalazine, balsalazide, olsalazine and mesalamine products after index date; reference category); short-term 5-ASA exposure (1 or more prescriptions of 5-ASA within 6 months after index date, and no additional 5-ASA prescription between 6–12 months after index date); and persistent 5-ASA exposure (1 or more prescriptions of 5-ASA within 0–6 months after index date, and between 6–12 months after index date). In distinction from prior studies, which described a patient as having continued vs. stopped 5-ASA based on new prescription of 5-ASA within 3 months after initiation of a biologic agents, we chose to define 3 exposure categories based on a 6–12 month window after index date.[14, 15] We chose a 6 month time period to define short term 5-ASA exposure because physicians that are treating patients with moderate to severe CD may be reluctant to stop 5-ASA within 3 months of starting a new agent to avoid confounding outcomes. We decided that persistent 5-ASA exposure would be defined as a group of patients with CD where the treating physician intended long term 5-ASA therapy. To allow for comparability with prior database studies that assessed 5-ASA exposure after escalation to biologic therapies in IBD, the secondary exposure categories were defined as stopping 5-ASA (no additional prescription of 5-ASA after index date; reference category) and continuing 5-ASA (1 or more prescription of 5-ASA within 3 months after index date).[14, 15]

Outcomes

The primary outcomes of interest were CD-related hospitalization or emergency department (ED) visit (CD as primary discharge diagnosis), CD-related surgery (classified using established procedural codes), new corticosteroid prescription, occurring at least 90 days after index date (to minimize confounding by disease severity), and treatment escalation (defined as switching to, or adding biologic agents or targeted small molecule inhibitors used to treat CD including infliximab, adalimumab, ustekinumab, vedolizumab or certolizumab pegol).

Patients were followed until occurrence of the outcome of interest, disenrollment from healthcare plan, treatment cessation (absence of new prescription for anti-metabolite agent for >120 days after last prescription), or completion of the study (last date of follow-up, June 30, 2019).

Covariates

Healthcare utilization, and comorbidities comprising surrogate markers of disease severity in the baseline period (prior to initiation of anti-metabolite agent) were classified as independent variables of interest. We evaluated baseline healthcare utilization on the proportion of patients with hospitalizations and ED visits, or abdominal surgery, in the baseline 12 months. The validated Elixhauser comorbidity index for administrative data was

used to measure comorbidity burden.[16] Any oral corticosteroid exposure in the previous 12 months was used as a surrogate measure of disease severity.

Statistical Analysis

The effectiveness of persistent and short-term 5-ASA use vs. stopping 5-ASA after escalation to anti-metabolite monotherapy was compared separately, using survival analysis with Kaplan-Meier curves, and Cox proportional hazard analysis, adjusting for age, sex, race, comorbidity burden, hospitalization or ED visit, abdominal surgery and corticosteroid use in the previous 12 months. Due to the exposure categories (persistent and short-term 5-ASA use) being defined after the index date, the exposures were at risk of immortal time bias. In order to reduce the risk of immortal time bias we used a 12-month landmark analysis. In this method, patients were considered at-risk of outcomes, only 12 months after index date; events occurring within 12 months after index date were recorded, but did not contribute to analysis.[17, 18] First we set the landmark time point t_{LM}, 12 months after the index time. Then, we created the "landmark dataset" by removing the patients with outcome events or censored before t_{LM}. Next, we created comparator groups based on the treatment status at t_{LM}. Last we performed the time-fixed Cox regression. We adopted the Landmark method because, distinctive from the alternative method of time-dependent Cox regression, it provides clinically clear comparisons and allows visualization by plotting Kaplan-Meier survival groups among comparators.[19, 20] A recent study of patients with CD who continued or discontinued 5-ASA after initiation of anti-TNF was designed to have outcome events occur after 90 days from the index date.[15]

Furthermore, to grant comparability with prior database studies of 5-ASA exposure after escalation to biologic therapies in IBD, we performed sensitivity analysis with two 5-ASA exposure categories (continued 5-ASA with prescription within 3m after index date vs. stopped 5-ASA) and performed 3-month landmark analysis (patients considered to be at-risk for outcomes only 3 months after index date), using Kaplan-Meier curves and Cox proportional hazard analysis.[14, 15]

Hazard ratio (HR) with 95% confidence intervals (CI) was calculated for each outcome of interest separately based on two-sided Wald test with a significance level of 0.05. All analysis was conducted in a secure Windows virtual machine provide by OptumLabs. We used DBVisualizer 10.0 (Stockholm, Sweden) for database management and R version 3.5.3 (Vienna, Austria) for statistical analysis.

Data Availability Statement

The data underlying this article were provided by OptumLabs by permission. Data will be shared on request to the corresponding author with permission of OptumLabs.

RESULTS

839,020 adult patients with CD or UC were identified in the database. After exclusion and inclusion criteria was applied, 3036 patients with CD who were new users of anti-metabolite monotherapy with 5-ASA use within 90 days before starting anti-metabolites were identified.

Patterns of 5-ASA users after initiation of anti-metabolites

Upon examination of 5-ASA prescription after initiation of anti-metabolites (index date), 667 (21.9%) patients “stopped 5-ASA”; 626 patients (20.6%) were classified as “short-term 5-ASA” users who received 5-ASA prescription within 6 months after index data, but without any 5-ASA prescription 6–12 months after index date, and 1743 patients (57.4%) were classified as “persistent 5-ASA” users who received 5-ASA prescription both within 6 months, and 6–12 months after index date implying there was an intention to continue 5-ASA long term after initiation of anti-metabolites (Figure 1).

No significant differences were observed in the baseline characteristics of patients based on exposure category (Table 1). The mean duration of follow up after index date ranged from 2.3 years in short term 5-ASA users to 3.2 years for persistent 5-ASA users. Overall, 38%−40% patients were hospitalized in the 12 months prior to index date, and 70%−77% had received corticosteroids. The majority of patients (>75%) had low comorbidity burden.

Comparative outcomes in patients who stopped 5-ASA vs short term 5-ASA use vs persistent 5-ASA use

Primary analysis was conducted with a 12-month landmark analysis to avoid immortal time bias. In this 12-month period after index date 64% patients with persistent 5-ASA use received corticosteroids, as compared to 60% patients with short term 5-ASA use and 55% patients who stopped 5-ASA. Approximately, 35%−40% patients were hospitalized for CD and approximately 4%−9% patients required CD related surgery. The majority of patients, >90% were continued on anti-metabolite monotherapy without need for escalation of therapy.

In follow up period after 12-month landmark, no significant difference was observed in time to CD-related hospitalization (P = 0.36, Figure 2A), CD-related surgery (P = 0.25, Figure 2B), or escalation of therapy (P = 0.59, Figure 2D) between patients who stopped 5-ASA, patients with short term 5-ASA use and patients with persistent 5-ASA use; however, patients with persistent 5-ASA use had significantly shorter time to initiation of corticosteroids as compared to patients who stopped 5-ASA (P = 0.002, Figure 2C).

On Cox proportional hazard analysis, adjusting for age, sex, race, comorbidity burden, and hospitalization or ED visit, abdominal surgery and corticosteroid use in the previous 12 months, as compared to patients who stopped 5-ASA, patients with persistent 5-ASA use had a higher risk of needing corticosteroids (HR, 1.24; 95% CI, 1.08–1.42), without any associated increase in the risk of CD-related hospitalization (HR, 1.21; 95% CI, 0.98–1.49), risk of CD-related surgery (HR, 1.28; 95% CI, 0.90–1.80), or need for escalation of therapy (HR, 0.85; 95% CI, 0.62–1.20) (Table 2). No differences were observed in patient who had short term use of 5 ASA as compared to those who stopped 5-ASA, at time of initiation of anti-metabolite monotherapy.

Sensitivity analysis using 3-month landmark analysis

Sensitivity analysis using a different definition of exposure (continued 5-ASA vs. stopped 5-ASA) and analytical approach (3-month landmark analysis) was performed. Features

of patients who continued vs. stopped 5-ASA are shown in eTable 1. Compared to the primary analysis, the 3-month landmark analysis had similar findings. No significant differences were observed in time to CD related hospitalization (P = 0.19, eFigure 2A), or CD related surgery (P = 0.48, eFigure 2B) between patients who stopped 5-ASA vs continued 5-ASA after initiation of anti-metabolite monotherapy. Patients who continued 5-ASA had significantly short time to initiation corticosteroids as compared to patient who stopped 5-ASA (P = 0.002, eFigure 2C). Unlike the primary analysis, patients who stopped 5-ASA had a shorter time to escalation of therapy than those who continued 5-ASA (P = 0.018, eFigure 2D). On Cox proportional hazard analysis, patients who continued 5-ASA had shorter time to need for corticosteroids, with no significant difference in the risk of CD-related hospitalization and CD-related surgery (eTable 2).

DISCUSSION

Despite the lack of evidence to support their efficacy, 5-ASAs continued to be the most commonly used medication for the treatment of CD in multiple jurisdictions worldwide.[21–24] Clinical guidelines recommend against the use of 5-ASA monotherapy for induction or maintenance of remission in patients with CD.[1, 3] However, their role as adjunctive therapy in patients with CD treated with immunosuppressive therapy is unclear, yet frequent. In this large retrospective cohort study, we observed that 57% of patients with CD who escalated to anti-metabolite-based therapy after failure of 5-ASAs, were continued on 5-ASAs for extended periods. Over a follow-up period of more than 2.5 years after starting anti-metabolites, continued use of 5-ASA was not associated with additional clinical benefit, such as decrease in the risk of CD-related hospitalization, surgery, relapse requiring corticosteroids or escalation to biologic-based therapy, as compared to stopping 5-ASA. Together with recent findings from Ungaro *et al* demonstrating lack of benefit of continued 5-ASA in biologic-treated patients with CD, these findings propose that continuation of 5-ASAs in patients who have escalated to immunosuppressive therapy for corticosteroid-dependent or moderate to severely active CD represents low-value care.[15]

Prior analyses of concomitant 5-ASA use in treatment of patients with IBD receiving thiopurines has suggested there are higher 6-TGN levels and lower 6-methylmercaptopurine/6-TGN ratios, which has been correlated with higher effectiveness of thiopurines.[8, 9, 25] However, these analyses have not demonstrated clinical efficacy when combining 5-ASA and thiopurines for the treatment of IBD. While we were unable to determine the effect of 5-ASA on thiopurine metabolite levels, we did not detected any clinical benefit among patients that continued 5-ASA versus those that stopped 5-ASA when escalating to anti-metabolite therapy. In a retrospective matched case control study from South Korea, Kwak *et al* compared concomitant 5-ASA and anti-metabolite therapy (n=318) to anti-metabolite monotherapy (n=106) among patients with CD. Over a median follow up of 4.8 years, they did not identify any difference in rates of corticosteroid use, escalation to biologic therapy, need for CD-related intestinal resection surgery or CD-related hospitalization.[26] Similarly, in a retrospective cohort of 104 patients with CD in remission on azathioprine, concomitant therapy with 5-ASA was not associated with reduced risk of clinical relapse.[27]

Contrary to our hypothesis, we observed that patients who continued on 5-ASA for >6 months after escalating to anti-metabolites had a higher risk of CD flare requiring corticosteroids, as compared to those who stopped 5-ASA. This finding is likely due to residual confounding by severity, as patients with trouble achieving remission with anti-metabolites, were more likely to be continued on 5-ASA, to avoid “rocking the boat”.

Given the limitations associated with our study design, the findings should be interpreted with caution. One such limitation is the observational nature of this study. As it was not an interventional study there may be unmeasured confounders across groups. This potential for unmeasured confounders by severity is important. The administrative data set used in this study did not include objective measures of disease severity (endoscopic or biochemical markers). As mentioned above, this limitation might explain some of the findings in our study. Similarly, though disease location may modify likelihood of response to 5-ASA in patients with CD, administrative claims codes have poor accuracy for identifying colon vs. ileum dominant disease.[28] It also remains unclear whether adding 5-ASA for patients with CD with persistent mild endoscopic activity despite optimization of anti-metabolite therapy may be beneficial. Though various formulations of 5-ASA that are released in different parts of the intestine are available and may have theoretical differences in efficacy, this data could not be analyzed since data on disease location was not accurate. Another limitation in our study is that the administrative claim codes used for both baseline covariates and outcomes could be subject to errors. The definitions of outcomes and covariates, such as treatment escalation and discontinuation etc. were selected by the investigators and were not validated. In addition, there was not detailed clinical information as to the reasoning for escalation to anti-metabolite therapy, continuation of 5-ASA or stopping 5-ASA. While 5-ASA is generally well tolerated, the safety outcomes among patients who continued versus stopped 5-ASA were not compared. While all patients in our study had received 5-ASA for a minimum of 3 months, which suggest tolerability, our study was not designed to assess safety. Separate analysis of mesalamine- and sulfasalazine-treated patients was not performed. Finally, the differences in early outcomes among patient who continued versus stopped 5-ASA was not examined as all outcomes in our study were compared >12 months after initiation of anti-metabolite therapy. While prior studies assessing biologic-treated patient examined early outcomes, our study used a 12-month landmark analysis to avoid misclassification of exposures and immortal time bias.[17] Due to the observational nature of our study, the definition of persistent 5-ASA use necessitated patients to have filled a prescription for 5-ASA between 0–6 and 6–12 months after initiation of immunomodulators. The patients in our study could not be classified as being short-term or persistent 5-ASA user at index date. As a result of this classification, patients who had continued 5-ASA use were unable to develop any adverse clinical outcomes because the exposure could not precede the outcome. We created a 3-month landmark analysis to evaluate outcomes after starting anti-metabolite therapy, the observed results were similar to the 12-month landmark analysis.

In conclusion, based on a large retrospective cohort study, 5-ASAs are commonly continued after escalation to anti-metabolite therapy in patients with CD, however they do not offer additional clinical benefit over stopping 5-ASA. An interventional randomized study of systematic withdrawal of 5-ASA in immunosuppressive-treated patients with

CD in remission is ongoing to definitively address this prevalent low-value practice (Stopping Aminosalicylate Therapy in Inactive Crohn's Disease (STATIC), NCT03261206). Additionally, further studies to examine whether adding 5-ASA for patients with CD with persistent mild endoscopic activity despite optimization of anti-metabolite therapy may be beneficial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest

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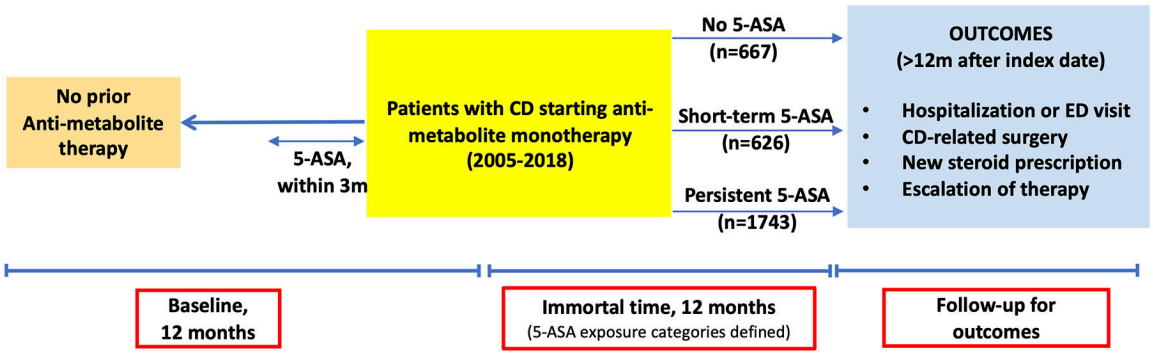
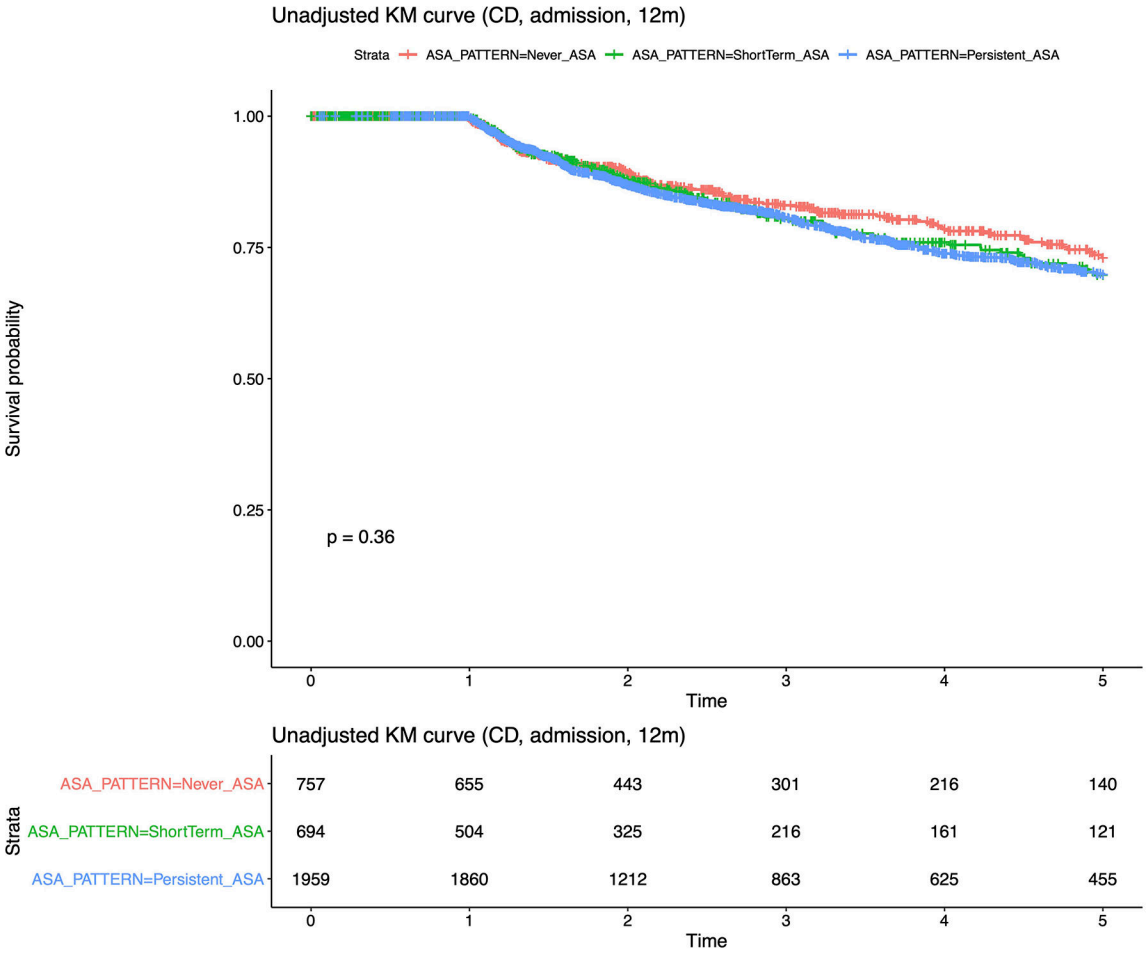
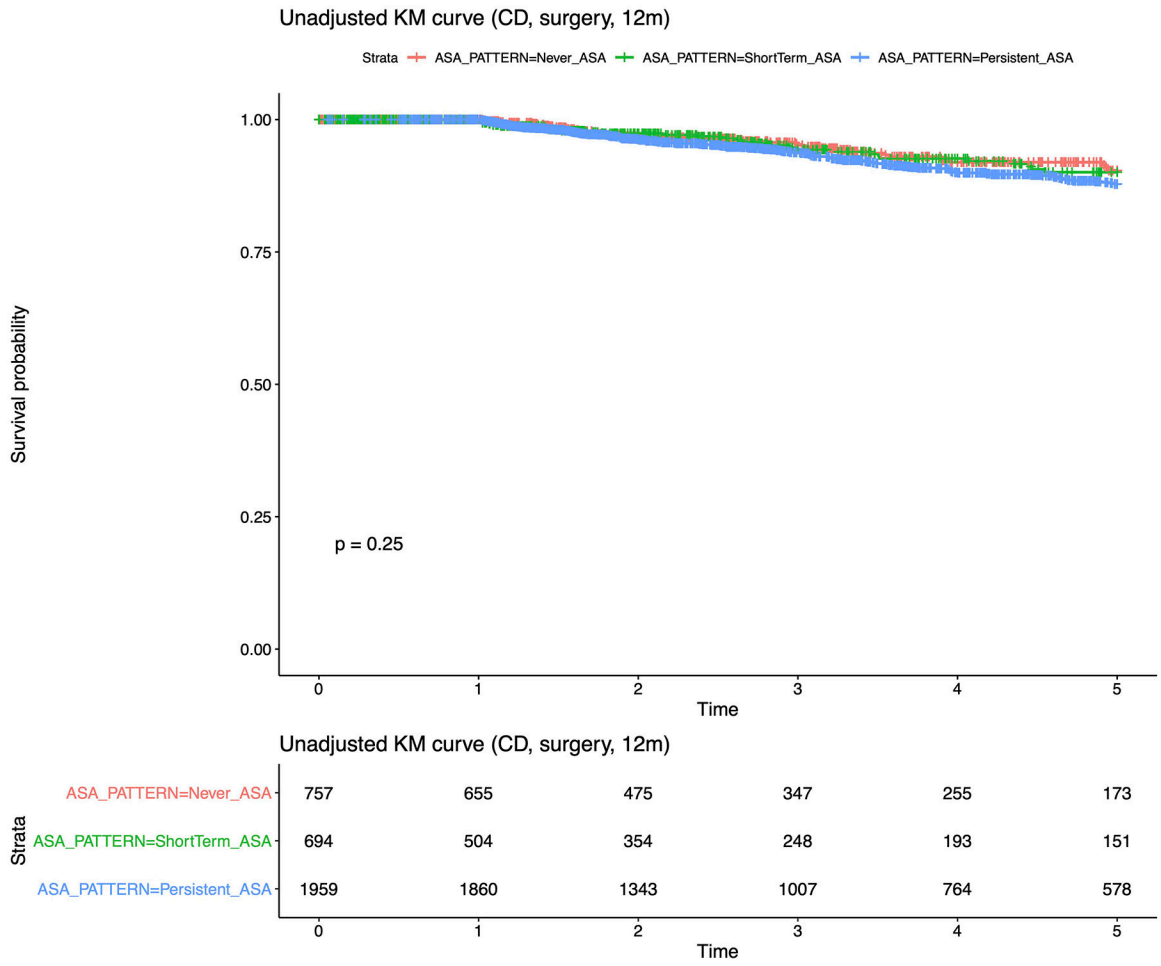
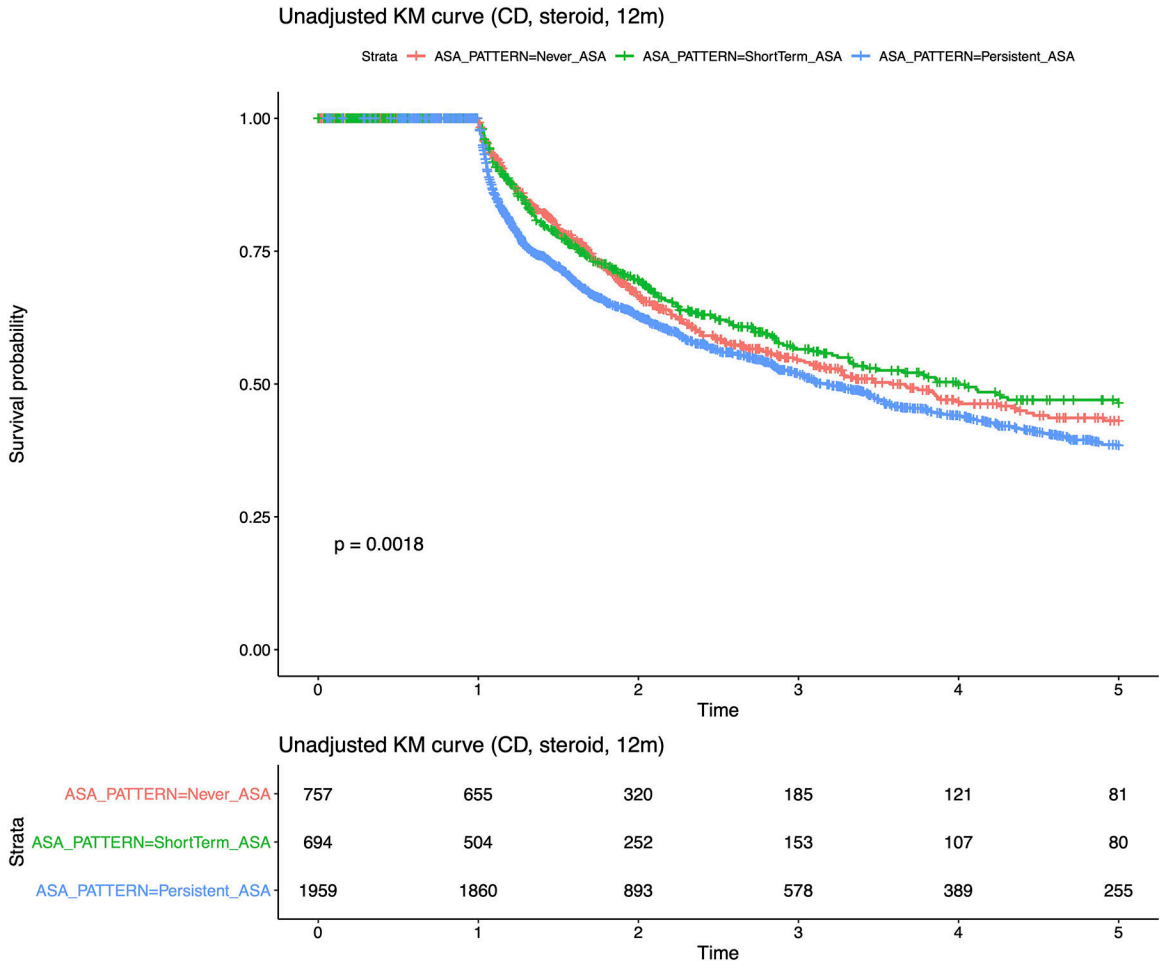


Figure 1.
Flow of patients for identification of anti-metabolite-treated patients with Crohn's disease







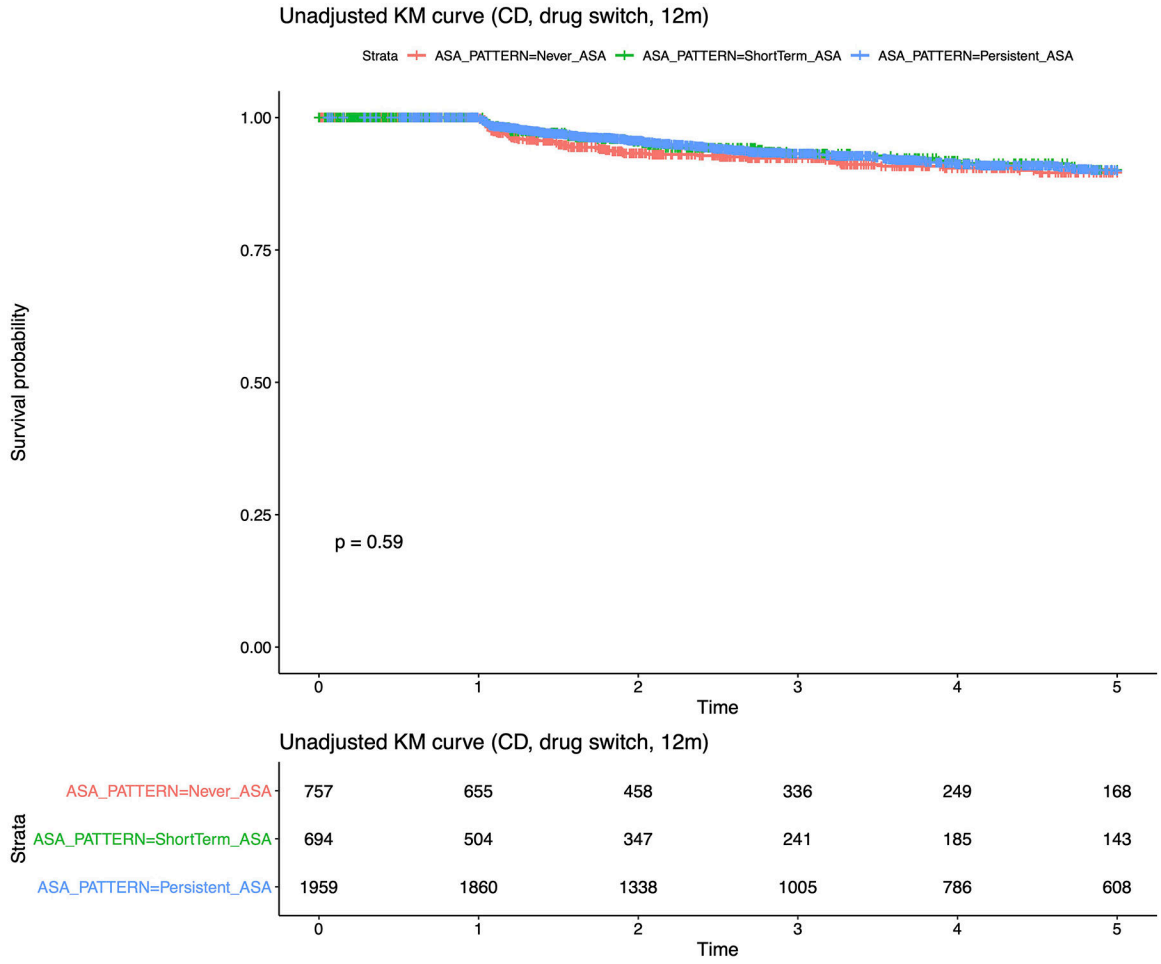


Figure 2.

Comparative effectiveness of stopping 5-ASA vs. short-term 5-ASA use vs. persistent 5-ASA use in anti-metabolite-treated patients with Crohn's disease, 12-month landmark analysis: (A) CD-related hospitalization and/or emergency department visit, (B) CD-related surgery, (C) Flare requiring corticosteroids and (D) Escalation of immunosuppressive therapy.

Table 1.

Baseline characteristics (and events during 0–12m immortal time after index date) of anti-metabolite-treated patients with Crohn's Disease at time of cohort entry, based on 5-ASA exposure category

Characteristics	Stopped 5-ASA (n=667)	Short-term 5-ASA (n=626)	Persistent 5-ASA (n=1743)
Age at index date (mean, SD)	36.2 (14.8)	34.3 (15.4)	36.6 (16.4)
Male sex, n (%)	288 (43.2%)	276 (44%)	880 (50.5%)
Race, White, n (%)	507 (76%)	486 (77.6%)	1300 (74.6%)
Follow-up after index date, in years (mean, SD)	2.8 (1.7)	2.3 (1.8)	3.2 (1.6)
Total person-year follow-up (from index date)	1854	1456	5552
Follow-up in at-risk period, in years (index date + 365d) (mean, SD)	1.8 (1.7)	1.3 (1.8)	2.2 (1.6)
BASELINE (Pre-index period), 0–12m BEFORE INDEX DATE			
Emergency department visits (n, %, with ≥1)	351 (53%)	346 (55%)	946 (54%)
Hospitalization (n, %, with ≥1)	261 (39%)	250 (40%)	667 (38%)
Abdominal surgery	85 (13%)	89 (14%)	207 (12%)
Steroids, within baseline 12m	466 (70%)	441 (70%)	1334 (77%)
Elixhauser Index (Mean, SD)	1.1 (6.6)	1.3 (6.2)	0.9 (5.8)
Number of comorbidities			
• None (0)	250 (37%)	222 (35%)	673 (39%)
• 1 or 2	289 (43%)	300 (48%)	773 (44%)
• 3 or more	128 (19%)	104 (17%)	297 (7%)
EVENTS OCCURING within 1–365d (0–12m) AFTER INDEX DATE			
Hospitalization or ED visit	255 (38%)	250 (40%)	623 (36%)
Surgery	49 (7%)	57 (9%)	81 (5%)
Steroid use	365 (55%)	378 (60%)	1120 (64%)
Escalation of therapy	51 (8%)	29 (5%)	74 (4%)

Table 2.

Incidence rate (per 100 person-years), and Cox proportional hazard analysis comparing outcomes in anti-metabolite-treated patients with Crohn's Disease, by 5-ASA exposure category (using 12m landmark analysis). Estimates that were statistically significant are highlighted in bold. Hazard ratios >1 indicate higher risk of outcome. Analyses were adjusted for age, sex, race, comorbidity burden, and hospitalization or emergency department visit, abdominal surgery and corticosteroid use in the previous 12 months

Outcomes	Analysis	Stopped 5-ASA	Short-term 5-ASA	Persistent 5-ASA
Hospitalization or ED visit	Incidence rate (per 100py)	5.8	6.4	6.8
	Adjusted HR with 95% CI	1.0 (reference)	1.15 (0.88–1.50)	1.21 (0.98–1.49)
CD-related surgery	Incidence rate (per 100py)	1.7	1.8	2.3
	Adjusted HR with 95% CI	1.0 (reference)	1.04 (0.64–1.7)	1.28 (0.90–1.8)
Corticosteroid use	Incidence rate (per 100py)	16.8	15.1	19.5
	Adjusted HR with 95% CI	1.0 (reference)	0.95 (0.79–1.13)	**1.24 (1.08–1.42)**
Escalation of therapy	Incidence rate (per 100py)	2.5	2.0	2.1
	Adjusted HR with 95% CI	1.0 (reference)	0.83 (0.54–1.3)	0.85 (0.62–1.2)