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ORIGINAL RESEARCH

Patterns of 6-mercaptopurine and azathioprine maintenance therapy among a cohort of commercially insured individuals diagnosed with Crohn's disease in the United States

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Background and aims: Thiopurines, including 6-mercaptopurine (6-MP) and azathioprine (AZA), are the mainstay of maintenance therapy for Crohn's disease (CD). However, studies examining their effectiveness in routine practice among diverse patient populations are lacking. Among a cohort of new users of 6MP/AZA, we described treatment patterns and changes in subsequent therapy.

Methods: Using the Truven Health Analytics databases, we identified all individuals diagnosed with CD and initiating 6-MP/AZA monotherapy from 2001–2008 (n=3,657). We estimated the proportion of CD patients remaining on 6-MP/AZA monotherapy, using Kaplan–Meier methods, and identified predictors of treatment noncontinuation, using multivariable Cox regression. Among the "noncontinuers," we described subsequent patterns of maintenance therapy and summarized the diagnosis and procedure codes and prescription drug claims preceding treatment discontinuation.

Results: The 1-year 6-MP/AZA treatment continuation rate was 42%. Children (age ≤18 years) and individuals with no prior anti-tumor necrosis factor (TNF) use were more likely to continue 6-MP/AZA, while those dispensed more (>4) outpatient prescriptions for any drug before initiation of 6-MP/AZA were less likely to continue maintenance treatment. Overall, 1,128 (39%) and 105 (4%) individuals experienced a clinical event potentially indicating active disease or 6-MP/AZA-intolerance prior to discontinuation, respectively. Most patients discontinued therapy; among the remaining patients who failed to continue 6-MP/AZA, most augmented with an anti-TNF.

Conclusion: Most patients initiating 6-MP/AZA monotherapy did not continue beyond 1 year. In contrast to trial evidence showing 1-year remission rates of 40%–80%, this study observed a lower effectiveness of 6-MP/AZA treatment, possibly due to differences in disease severity, patient demographics, comorbidity, adherence, and health care utilization.

Keywords: immunomodulators, outcomes research/measurement, inflammatory bowel disease, patterns of care

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) affecting close to 500,000 Americans.[1,2] CD is characterized by flares of abdominal pain, diarrhea, rectal bleeding, and extraintestinal manifestations, followed by periods of remission. Because the disease is typically relapsing and remitting, the two goals of medical therapy are to treat disease flares and prolong remission.

Since the initial trial conducted by Present et al in 1980 describing the efficacy of 6-mercaptopurine in (6-MP) in the treatment of CD, thiopurines, including 6-MP and azathioprine (AZA), have become mainstays in the IBD therapeutic arsenal.[3–5]

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Subsequent randomized controlled trials (RCTs) have reported 1-year remission rates for 6-MP/AZA in adult CD populations of 40%–70%;[6–9] and a single RCT in pediatric CD demonstrated a >80% remission rate at 12 and 18 months.[10] Consequently, a recent meta-analysis from the Cochrane Collaboration concluded that thiopurines are effective for inducing and maintaining remission among adult CD patients.[4]

In addition to RCTs, which are the gold standard for evaluating treatment efficacy, clinical effectiveness research involves the study of the benefits and harms of medications when used in "real-world" settings, in which patients tend to be older, have more comorbidity,[11] are not as carefully monitored or adherent to their medications, and remain on treatment longer than subjects in RCTs.[12] An early study by Fraser et al[13] using 30 years of data from an IBD clinic in Oxford, England reported overall rates of remission in CD patients initiating AZA of 45% (123/272), consistent with, though on the low end of, RCT findings. However, data from more recent studies examining the real world use of 6-MP/AZA have suggested that the clinical effectiveness of thiopurines in practice may be less than the efficacy demonstrated in clinical trials. A study by Goodhand et al[14] reported that 6-month steroid-free remission was achieved in only 30% (15/50) of children and 38% (19/50) of adults treated with thiopurines. Another study, by Riello et al,[15] found similar rates of steroid-free remission in a small, single-center observational pediatric cohort of CD patients. Most recently, an observational study by Hyams et al[16] reported that children who initiated immunomodulator treatment had similar rates of remission at 1 year when compared with children who did not initiate immunomodulator or anti-tumor necrosis factor (TNF) treatment, indicating a lack of effectiveness.

To further evaluate the clinical effectiveness of thiopurines in a large and diverse population, we used health insurance claims data in the USA to undertake a retrospective cohort study of individuals diagnosed with CD who initiated 6-MP/AZA monotherapy. Specifically, we estimated the proportion of CD patients that remained on this maintenance regimen over time and identified independent patient-level predictors of 6-MP/AZA monotherapy noncontinuation. We also described clinical events occurring before discontinuation, and examined the subsequent treatment strategies utilized.

Materials and methods

Data source

The data for this study were drawn from Truven Health Analytics databases (Ann Arbor, MI, USA), including the Commercial Claims and Encounters database (January 1, 2000 – December 31, 2009) and the Medicare Supplemental and Coordination of Benefits database (January 1, 2006 – December 31, 2009), collectively referred to as "the databases." The databases capture person-specific clinical utilization, expenditures, and enrollment information across inpatient, outpatient, prescription drug, and carve-out services from a selection of large employers, health plans, and government and public organizations in the USA. The paid claims and encounter data for the study period were linked to detailed patient information across sites and types of providers, and over time. The annual medical databases include commercial health data from approximately 100 payers.

Inpatient and outpatient diagnoses and procedures were recorded using International Classification of Diseases, ninth revision (ICD-9 CM) codes, Common Procedural Terminology (CPT) codes, and Healthcare Common Procedure Coding System (HCPCS) codes. Drug information, including administration and the dispensing of specific treatments, were identified using HCPCS codes and National Drug Codes (NDCs).[17] Patient demographic data, and start and stop dates for plan enrollments were recorded. As all records used in the analysis were previously collected and deidentified, this study did not constitute human subjects research.

Study sample

All individuals with a first prescription claim for 6-MP/AZA between January 1, 2001 and December 31, 2008 were eligible for study inclusion. The date of the first 6-MP/AZA prescription claim was defined as the "index prescription date." Each individual was required to have plan enrollment for at least 12 - months prior to ("preindex period") and following ("postindex period") the index prescription date, creating a cohort of incident users of 6-MP/AZA with sufficient health care utilization information to assess the important predictors and outcomes of interest.[18] To ensure that the study population included only CD patients, individuals were only included if they had at least two claims for CD (ICD-9: 555) on different days and no claims for ulcerative colitis (UC) (ICD-9: 556) during the preindex period. To ensure a study population in which 6-MP/AZA monotherapy was the primary maintenance strategy, all individuals who used other CD treatment (ie, methotrexate, an anti-TNF agent, or natalizumab) during the 90-day "washout period" prior to the index prescription date were excluded.

Outcome definitions

Treatment continuation

Because administrative data lack the detail necessary to identify all clinically relevant outcomes, including

disease exacerbations, changes in disease activity, and medication-related toxicity, the primary outcome for this study, determined a priori, was the continuation of 6-MP/AZA as the primary treatment strategy. This is an appropriate proxy outcome for clinical effectiveness because patients who discontinue 6-MP/AZA, who augment their treatment with another agent, or who switch agents are likely either intolerant to or "failures of 6-MP/AZA." Treatment continuation was defined as continuous 6-MP/AZA monotherapy (without concurrent use of other CD maintenance treatment, such as methotrexate, anti-TNF agents, or natalizumab). The period of use was determined by the date of 6-MP/AZA dispensing, plus days supplied, plus an additional 90-day "grace" period to account for delays in prescription dispensing or poor adherence. If the number of days supplied was missing, it was assumed to be 30 days.

Treatment augmentation, switch, and discontinuation

Three mutually exclusive secondary outcomes were defined, which together accounted for the failure of treatment continuation (Figure 1). The first category was a "treatment augmentation," defined as the presence of a claim for methotrexate, an anti-TNF agent, or natalizumab (a "new maintenance treatment") occurring alongside continuous 6-MP/AZA treatment, allowing for a 90-day grace period. The date of augmentation was defined as the date of the first new maintenance treatment claim. The second category was a "treatment switch," defined as the presence of a claim for a new maintenance treatment in addition to the lack of a claim for 6-MP/AZA during the period from the date of the new maintenance treatment plus the number of days supplied and a 90-day grace period. The date of switch was the date of the first new maintenance treatment claim. The third outcome was a "treatment discontinuation," defined as the lack of a claim for any maintenance treatment (ie, 6-MP/AZA or a new maintenance treatment) during the period from the date of last prescription claim for 6-MP/AZA plus the days supplied and a 90-day grace period. The date of discontinuation was the date of the last 6-MP/AZA claim plus the days supplied. All remaining individuals were considered to be censored either at disenrollment from the health plan or at the end of the study period (December 31, 2009).

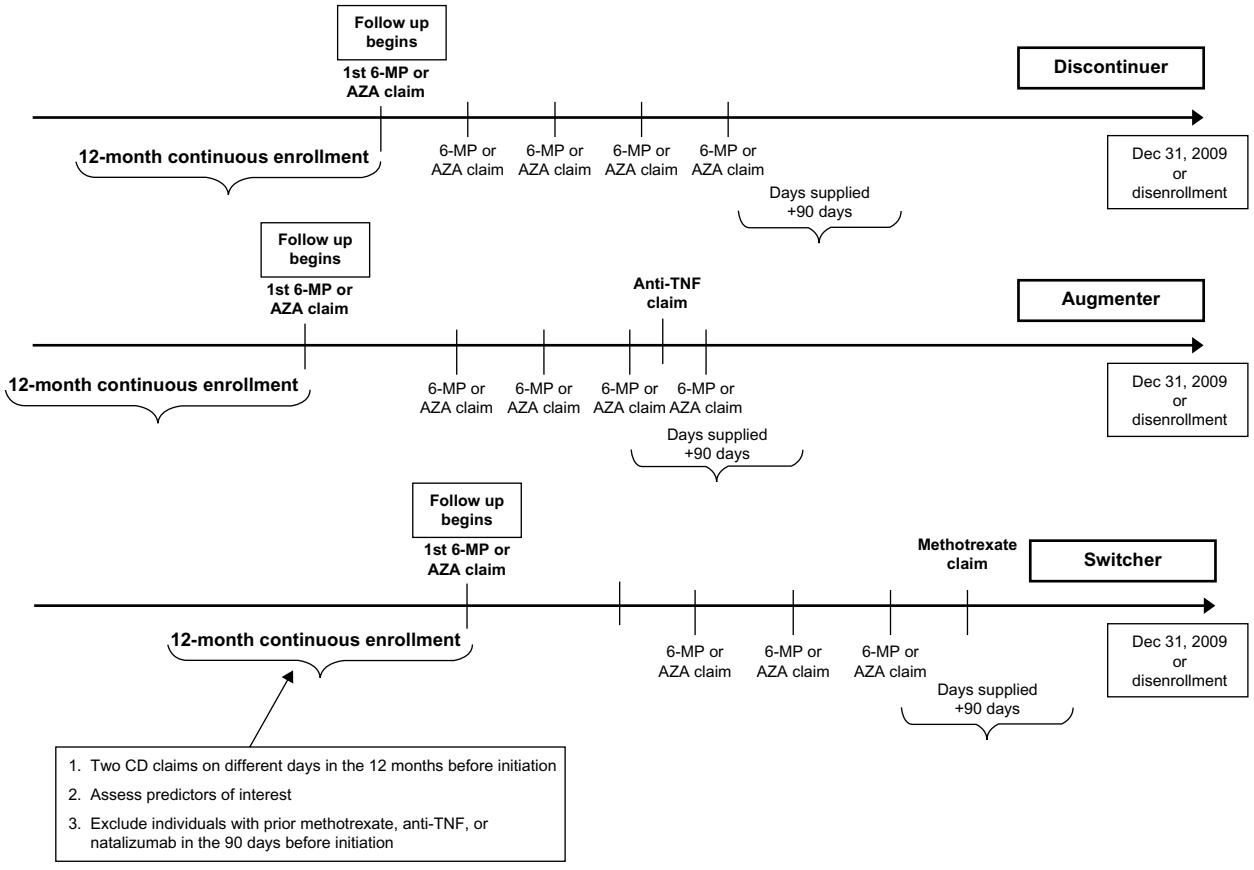

Figure 1 Illustration of the cohort of CD patients who initiated 6-mercaptopurine/azathioprine, and the three secondary outcomes of treatment, discontinuation, augmentation, and switch.

Abbreviations: 6-MP, 6-mercaptopurine; AZA, azathioprine; CD, Crohn's disease; TNF, tumor necrosis factor.

Patient-level predictors

Data on patient characteristics that were hypothesized to be independently associated with failure to continue 6-MP/AZA treatment were obtained from the inpatient, outpatient, and pharmacy claims during the 12-month preindex period. The demographic information included age (at the index prescription date), sex, and region of residence (Northeast, North Central, South, and West). Treatment-related variables included the year of 6-MP/AZA initiation and prior corticosteroid, 5-aminosalicylate (5-ASA), and antibiotic use during the preindex period. Prior methotrexate, anti-TNF, and natalizumab use was assessed during the 9 months prior to the 90-day washout period. Other measures, of comorbid illness and health care utilization, measured during the preindex period included the Charlson comorbidity score (0, 1, ≥2),[19] a prior diagnosis of rheumatologic disease or other autoimmune disease (including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, juvenile idiopathic arthritis, and multiple sclerosis), the number of unique outpatient visits, the number of unique outpatient gastrointestinal visits, the number of unique generic drug prescriptions (a marker of health care utilization), the number of unique gastrointestinal procedures, and the number of unique hospitalizations (occurring at least 2 days apart) with a CD discharge diagnosis.

Clinical events occurring prior to study outcomes

In an exploratory analysis, we summarized the diagnosis codes and procedure and outpatient pharmaceutical claims occurring prior to the study outcomes. We defined two broad categories of events that might indicate intolerance to the initial 6-MP/AZA treatment or active disease. "Possible indicators of intolerance" included a diagnosis of pancreatitis, liver toxicity, or low white blood cell count during the 60-day period prior to reaching any of the above study endpoints (augmentation, switch, or discontinuation). "Possible indicators of active disease" included a prescription for an oral steroid, a gastrointestinal surgical procedure, or a hospitalization with a primary discharge diagnosis of CD within the 60 days prior to any of the above endpoints. The period of 60 days was selected based on clinical input. All the ICD-9 diagnosis and procedure codes, NDCs, and HCPCS codes used to define the study outcomes are listed online (Tables S1 and S2).

Statistical analysis

We utilized nonparametric Kaplan–Meier survival analysis to estimate the time-to-event (failure to continue 6-MP/AZA monotherapy) among the cohort of CD patients initiating 6-MP/AZA between January 1, 2001 and December 31, 2008. Descriptive statistics were generated to report the mean and interquartile range of the time-to-treatment failure. We estimated the 1-year event-free rate, defined as the proportion of the cohort remaining on their initial continuous 6-MP/AZA therapy at 1-year postinitiation and reported this for the cohort overall and stratified by children (≤18 years) and adult (>18 years) populations. We performed multivariable Cox proportional hazards regression to identify patient-level predictors that were independently associated with failure to continue 6-MP/AZA. Our models estimated unadjusted and adjusted hazard ratios (HRs) (controlling for all other predictors) and 95% confidence intervals (CIs) for all the predictors of interest. As 8–16 weeks of 6-MP/AZA treatment are required in order to obtain pharmacokinetic effects, we conducted a subanalysis examining the effectiveness of initial 6-MP/AZA treatment among the CD patients remaining on monotherapy for at least 3 months.

For individuals failing to continue 6-MP/AZA monotherapy, we reported the number and proportion of individuals who started on alternative treatment strategies. Finally, we summarized the number and proportion of diagnosis and procedure codes and outpatient prescription drug claims for the clinical events occurring 60 days prior to the failure of treatment continuation that possibly indicated either 6-MP/AZA treatment intolerance or active CD. All the statistical analyses were conducted using SAS version 9.2 (Cary, NC, USA).

Results

Study population

The study sample comprised 3,657 individuals with a diagnosis of CD initiating 6-MP/AZA therapy from January 1, 2001– December 31, 2008, with a median follow up of 2.5 years (interquartile range 1.6, 4.0). Table 1 reports the demographic and clinical characteristics of the cohort. Children (aged 0– 18 years) accounted for 16% of the study sample, while those aged 60 years and older made up approximately 11%. The majority of the individuals in the cohort were women (54%) and most frequently lived in the South (40%). Prior to 6-MP/AZA initiation, the use of methotrexate (<1%) and anti-TNFs (2%) was rare; however, the majority of individuals in the cohort used corticosteroids (59%), 5-ASAs (72%), and antibiotics (64%).

Rates and predictors of treatment noncontinuation

Figure 2 illustrates the nonparametric Kaplan–Meier curve estimating the time-to-noncontinuation among the cohort of

Table 1 Characteristics of 3,657 Crohn's disease patients initiating 6-MP/AZA from 2001–2008

Characteristic	Number of patients	Percentage of patients
Female	1,986	54.3%
Male	1,671	45.7%
Age (mean, SD)	42 (16.77)	
0 to 18	575	15.7%
19 to 29	537	14.7%
30 to 39	618	16.9%
40 to 49	719	19.7%
50 to 59	809	22.1%
≥60	399	10.9%
Region[a]		
Northeast	443	12.1%
North Central	1,167	31.9%
South	1,463	40.0%
West	574	15.7%
Prior drug use[b]		
Methotrexate	17	0.5%
Anti-TNFs	68	1.9%
Concomitant drug use[c]		
Corticosteroids	2,149	58.8%
5-ASAs	2,637	72.1%
Antibiotics	2,333	63.8%
Measures of comorbidity		
Charlson score, 0	2,903	79.4%
Charlson score, 1	484	13.2%
Charlson score, ≥2	270	7.4%
Prior rheumatologic condition	120	3.3%
Number of GI outpatient visits		
0 visits	1,128	30.8%
1 to 2 visits	871	23.8%
≥3 visits	1,658	45.3%
Number of distinct generic drug prescriptions		
1 to 4	523	14.3%
5 to 8	1,153	31.5%
9 to 12	973	26.6%
≥13	1,008	27.6%

Notes: [a]Region was missing for ten individuals; [b]prior use was defined as occurring during the 3–12 months prior to 6-MP/AZA initiation; [c]concomitant use was defined as occurring during the 12 months prior to 6-MP/AZA initiation.

Abbreviations: 5-ASA, 5-aminosalicylate; 6-MP, 6-mercaptopurine; AZA, azathioprine; GI, gastrointestinal; SD, standard deviation; TNF, tumor necrosis factor.

CD initiators of 6-MP/AZA over time (measured in months from initiation). Nearly one-quarter of individuals in the cohort did not continue 6-MP/AZA monotherapy longer than 2 months. Similarly, more than 50% and 75% of individuals in the cohort failed to continue 6-MP/AZA treatment for 8 months and 28 months, respectively. The overall 1-year continuation rate of 6-MP/AZA monotherapy was 42%. Stratified by age group, the 1-year continuation rate was 54% for children (≤18 years) and 41% for adults (>18 years). For individuals with prior anti-TNF use, the 1-year continuation rate was 22%. Among the individuals who continued on 6-MP/AZA treatment for 3 or more months, the continuation rate at 12, 18, and 24 months was 63%, 50%, and 42%, respectively. The median follow up among CD patients after failure to continue 6-MP/AZA was 2.03 years (interquartile range 1.20–3.42).

We estimated unadjusted and adjusted HRs (aHRs) and 95% CIs for the association between each patient-level predictor of interest and initial 6-MP/AZA treatment failure (Table 2), using multivariable Cox proportional hazards regression. The individuals who used anti-TNFs prior to their initial 6-MP/AZA prescription were more likely to fail to continue on treatment compared with those who did not (aHR =1.64, 95% CI: 1.26, 2.13). Age appeared to have a nonlinear association with noncontinuation, where individuals aged 19–29, 30–39, and 40–49 years all had an elevated hazard compared with individuals aged 0–18 years, while older adults aged 50–59 and ≥60 years did not. When age was dichotomized (age ≤18 vs >18 years), adults were more likely than children to fail to continue on 6-MP/AZA (aHR =0.85, 95% CI: 0.76, 0.95). Having a diagnosis of a rheumatologic or other autoimmune disease with an indication for an anti-TNF prior to 6-MP initiation increased the hazard of treatment noncontinuation (aHR =1.23, 95% CI: 1.00, 1.51). Lastly, individuals receiving a higher number of unique generic prescription drug fills in the year prior to their 6-MP/AZA initiation (5–8, 9–12, and ≥13 vs 1–4 unique generic prescriptions) were more likely to fail to continue 6-MP/AZA monotherapy.

Subsequent maintenance therapy strategy changes

Table 3 reports the number and proportion of the 2,845 individuals who did not continue on 6-MP/AZA monotherapy and who changed to another maintenance therapy strategy. A total of 484 individuals (17%) augmented their 6-MP/AZA treatment with an anti-TNF agent. Almost 9% discontinued 6-MP/AZA and switched to another CD strategy, such as methotrexate alone (1.6%), an anti-TNF alone (7%), or an anti-TNF in combination with methotrexate (<1%). Most CD patients (n=2,108 or 74%) completely discontinued 6-MP/AZA without augmenting or switching.

Possible indicators of 6-MP/AZA intolerance or active disease

Among individuals who did not continue on 6-MP/AZA monotherapy (n=2,845), Table 4 reports the number and proportion of patients who received a diagnosis, procedure, or prescription for clinical events, which could indicate a

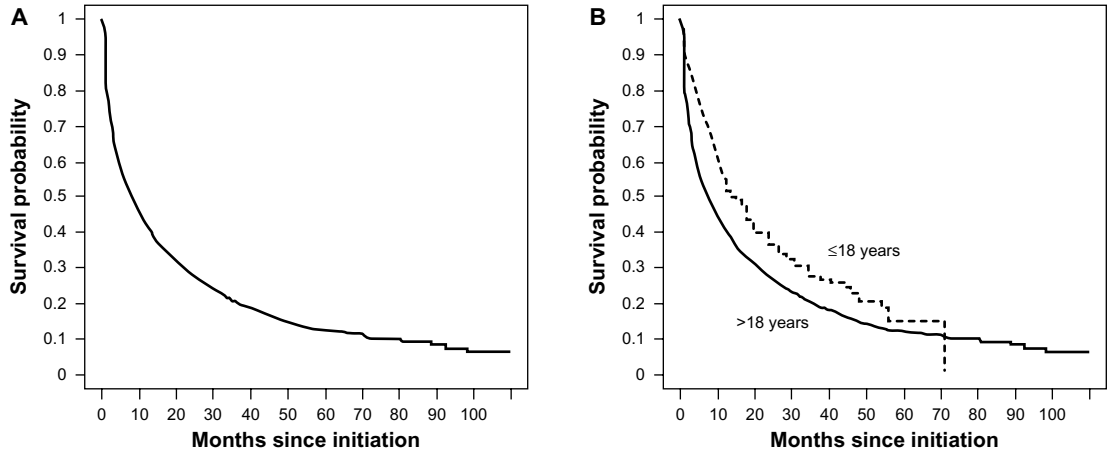

Figure 2 Time-to-treatment noncontinuation of initial 6-MP/AZA maintenance therapy.
Notes: Nonparametric Kaplan–Meier survival curves estimate the time-to-noncontinuation of initial 6-MP/AZA maintenance therapy among a cohort of CD patients (n=3,657) initiating 6-MP/AZA maintenance therapy between January 1, 2001 and December 31, 2008, overall (**A**) and stratified by age (≤18 vs >18 years), (**B**). At 12, 24, and 36 months, the numbers of CD patients at risk were 1,544, 730, and 352. Stratified by age, the same numbers of patients at risk were 170, 67, and 32 and 1,374, 663, and 320 among those ≤18 years and >18, respectively.
Abbreviations: 6-MP, 6-mercaptopurine; AZA, azathioprine; CD, Crohn's disease.

Table 2 Patient-level predictors of failure to continue initial 6-MP/AZA among 3,657 Crohn's disease patients

Independent variable	Unadjusted HR (95% CI)	Adjusted HR[c] (95% CI)
Female vs male	0.87 (0.81–0.93)	0.92 (0.85–0.99)
19–29 years vs 0–18 years	1.47 (1.28–1.68)	1.39 (1.21–1.59)
30–39 years vs 0–18 years	1.35 (1.19–1.54)	1.25 (1.09–1.43)
40–49 years vs 0–18 years	1.27 (1.12–1.43)	1.16 (1.02–1.32)
50–59 years vs 0–18 years	1.17 (1.03–1.32)	1.04 (0.91–1.19)
≥60 years vs 0–18 years	1.20 (1.04–1.40)	1.07 (0.91–1.25)
Northeast vs South	0.81 (0.72–0.92)	0.86 (0.76–0.97)
North Central vs South	0.90 (0.82–0.98)	0.91 (0.84–1.00)
West vs South	0.93 (0.83–1.03)	0.95 (0.85–1.07)
Anti-TNF prescription prior to initiation[a] (yes vs no)	1.81 (1.40–2.33)	1.64 (1.26–2.13)
Methotrexate prescription prior to initiation[a] (yes vs no)	1.35 (0.82–2.25)	1.21 (0.73–2.03)
Salicylate prescription prior to initiation[b] (yes vs no)	0.96 (0.88–1.04)	0.94 (0.86–1.02)
Steroid prescription prior to initiation[b] (yes vs no)	1.00 (0.93–1.08)	0.95 (0.88–1.03)
Antibiotic prescription prior to initiation (yes vs no)	1.19 (1.10–1.28)	1.06 (0.96–1.16)
History of rheumatologic disease[b] (yes vs no)	1.27 (1.04–1.55)	1.23 (1.00–1.51)
5–8 vs 1–4 generic prescriptions[b]	1.16 (1.03–1.31)	1.20 (1.05–1.37)
9–12 vs 1–4 generic prescriptions[b]	1.24 (1.09–1.40)	1.28 (1.10–1.49)
≥13 vs 1–4 generic prescriptions[b]	1.43 (1.27–1.62)	1.46 (1.23–1.73)

Notes: [a]Prior use was defined as occurring during the 3–12 months prior to 6-MP/AZA initiation; [b]all variables were assessed during the 12 months prior to 6-MP/AZA initiation; [c]all estimates were adjusted for all the variables above in addition to year of initiation, Charlson score, number of office visits, number of gastrointestinal procedures, and number of hospitalizations.
Abbreviations: 6-MP, 6-mercaptopurine; AZA, azathioprine; CI, confidence interval; HR, hazard ratio; TNF, tumor necrosis factor; vs, versus.

possible intolerance to 6-MP/AZA or active disease flare. Overall, 105 individuals (4%) received diagnoses that could indicate a possible intolerance, including a diagnosis for pancreatitis (2%), liver toxicity (1%), and low white blood cell count (1%). Similarly, 1,128 individuals received diagnoses, procedures, or prescriptions for clinical events that could indicate an active disease flare (39%), including a prescription for an oral steroid (27%), a gastrointestinal-related procedure (16%), and hospitalization with a CD-related discharge diagnosis (8%). Almost 2% of the cohort experienced both indicators during the study period.

Discussion

An examination of the patterns and effectiveness of 6-MP/AZA treatment for maintenance of CD remission is important because patients treated in the routine setting are different to those enrolled in RCTs. In this retrospective cohort of

Table 3 Maintenance therapy changes among 2,845 patients diagnosed with Crohn's disease who failed to continue initial 6-MP/AZA therapy

Treatment strategy	Number of patients (%)
Discontinued all therapy	2,108 (74.02)
Switched to another therapy	
Natalizumab	0 (0.00)
Methotrexate	45 (1.58)
Anti-TNF	203 (7.13)
Anti-TNF + methotrexate	5 (0.18)
Augmented with another therapy	
6-MP/AZA + anti-TNF	484 (16.99)

Abbreviations: 6-MP, 6-mercaptopurine; AZA, azathioprine; TNF, tumor necrosis factor.

Table 4 Clinical events occurring among 2,845 CD patients during the 60 days prior to failure of initial 6-MP/AZA treatment continuation

Event of interest	Number of patients (%[a])
Possible indicator of intolerance	105 (3.6)
Pancreatitis diagnosis	71 (2.4)
Liver toxicity diagnosis	17 (0.6)
Low white blood cell count diagnosis	18 (0.6)
Possible indicator of active disease	1,128 (38.6)
Oral steroid prescription	799 (27.4)
GI surgery procedure	480 (16.4)
Hospitalization related to CD	246 (8.4)
Both	56 (1.9)

Notes: [a]Individuals can experience multiple events in each category, therefore the column percentages do not sum to 100%.
Abbreviations: 6-MP, 6-mercaptopurine; AZA, azathioprine; CD, Crohn's disease; GI, gastrointestinal.

3,657 individuals with CD initiating on 6-MP/AZA (98% of whom were immunomodulator or biologic naïve), we found that approximately 42% of the CD patients who initiated 6-MP/AZA monotherapy remained on this treatment strategy after 1 year, and only 28% remained at 2 years. When restricted to patients who remained on therapy for at least 3 months (an adequate amount of time to achieve pharmacokinetic effects), 63% and 42% remained on their 6-MP/AZA without augmenting or switching at 1 and 2 years, respectively. Taken together, these data suggest that most individuals benefit from 6-MP/AZA monotherapy at 1 year; however, the longer-term benefits remain uncertain, and our data do not allow us to comment directly on these benefits. Despite this uncertainty, many clinical algorithms recommend this approach, and it has become a mainstay of medical therapy for moderate to severe CD.[20,21]

Because the primary outcome of our study, treatment continuation, is different than the clinical outcomes of disease remission or steroid-free remission used in clinical trials and retrospective chart reviews, direct comparisons with the existing literature are not possible. However, as treatment continuation may either over- or underestimate clinical remission, we believe that, on balance, it is a reasonable proxy indicator. Treatment continuation will overestimate remission in instances where patients remain on 6-MP/AZA despite active disease, or may underestimate clinical remission in instances where discontinuation occurs due to poor adherence or other reasons aside from treatment failures.

Our findings are in line with emerging evidence suggesting that the real-world clinical effectiveness of 6-MP/AZA may be somewhat lower than the efficacy initially observed in randomized trials. The Cochrane Collaboration conducted a meta-analysis of eight published randomized, double-blind, placebo-controlled trials of AZA or 6-MP therapy in adult patients (≥19 years) with CD[4] and concluded that both treatments were effective in maintaining the remission of CD, with a summary odds ratio (OR) in the AZA trials of 2.32 (95% CI: 1.55, 3.49) and in the 6-MP trials of 3.32 (95% CI: 1.40, 7.87). The 1-year remission rates reported in these trials ranged from 40%–70%.[6–9] The Markowitz et al pediatric study[10] showed similar, if not higher, efficacy, with >80% of children in remission at 1 year. However, the success of 6-MP/AZA when used in clinical practice has not been consistently documented in the literature. The 30-year retrospective study by Fraser et al[13] investigating 272 patients from an IBD referral center in Oxford, England reported the rate of overall remission (defined as being steroid-free for at least 3 months) was 45%, which increased to 64% among CD patients who completed 6 or more months of treatment. Two small observational studies have shown relatively low clinical effectiveness of 6-MP/AZA in pediatric CD in clinical settings. Riello et al[15] conducted a retrospective observational cohort study of AZA effectiveness in 105 pediatric CD patients from a single center in Paris, France. Remission (as measured by a pediatric CD activity index ≤10 without any steroid medication) at 12 months of follow up occurred in only 40% of patients. More recently, Hyams et al[16] drew upon a multicenter, inception cohort to compare 1-year remission outcomes for initiators of anti-TNFs, initiators of immunomodulators, and children who did not initiate immunomodulator therapy. After propensity score matching, the authors found no comparative benefit of initiating immunomodulators versus not receiving treatment (OR: 1.3, 95% CI: 0.6, 2.8). Therefore, our findings in a larger and more diverse sample are consistent with this emerging literature regarding real-world clinical effectiveness.

One particularly notable finding from our study was the effects of age on length of treatment continuation. Children had longer periods of treatment continuation than did adults, which may indicate a higher response to 6-MP/AZA in the pediatric versus adult populations. Increased efficacy of 6-MP/AZA in the pediatric population was suggested by the Markowitz study,[10] where it was hypothesized that treatment earlier in the course of the disease may be a potential disease-modifying strategy.[22] Another possible explanation for the longer treatment continuation among children observed here is that children may experience less toxicity than adults, as has been suggested by a small, single-center retrospective study by Goodhand et al,[14] which found that 6-MP/AZA was better tolerated in children than adults (albeit with no

difference in efficacy). Finally, nonmechanistic reasons may also explain the elevated continuation in children, where parents' involvement in the management of their child's disease may improve adherence. We also noted that individuals initiating 6-MP/AZA in older age (≥50 years) were at a reduced hazard of treatment noncontinuation compared with other adults (19–49 years), consistent with the findings by Fraser et al.[13] This may indicate that 6-MP/AZA is more effective in older individuals, or may reflect differences in disease course, adherence, and/or insurance coverage in the elderly in the USA.

An additional finding worth highlighting is that although prior anti-TNF users were less likely to continue on long-term 6-MP/AZA monotherapy than were anti-TNF naïve patients, approximately 22% continued on thiopurines for longer than 1 year. This suggests that the long-term benefits of sequential therapy with anti-TNF inhibitors followed by thiopurines in "anti-TNF failures" may equal the benefits of the combination of anti-TNF and thiopurines initiated simultaneously, as has recently been suggested by Lewis.[23]

We were surprised that 2,108 (74%) of all treatment failures were considered discontinuations of treatment. Accordingly, we performed a series of analyses to further examine the discontinuers and exclude the possibility of misclassification of either CD itself or medication discontinuation. Approximately, 57% of those that discontinued had claims with an ICD-9 diagnosis code for CD within 90 days of 6-MP/AZA discontinuation, and 86% had CD claims at any point following 6-MP/AZA discontinuation, suggesting that these patients did, in fact, have CD and received ongoing care for their condition. In the 90 days following all maintenance treatment discontinuation, we found that 12% (n=259) had a claim for hospital admission, 5% (n=96) had a claim for a gastrointestinal-related surgery, and 0.3% (n=6) had a claim for cyclosporine, tacrolimus, or mycophenolate, which could be indicative of a maintenance treatment failure. However, in the same time period, we identified 674 individuals (32%) who had a prescription for 5-ASA or sulfasalazine, which would be consistent with a "step down" strategy due to improvements in disease course. As such, these data suggest that discontinuers comprise a heterogeneous group of patients. Indeed, our findings of medication nonuse are consistent with the findings of a recent population-based study by Melesse et al,[24] which used the University of Manitoba IBD Epidemiology Database linked to an outpatient prescription drug database. Researchers found that by the end of 5 years, only 46% of CD patients continued to use IBD medications.

Because our study relied upon administrative data, there are several limitations to consider when interpreting the results. One key issue discussed previously is the use of the outcome variable, continuation of 6-MP/AZA monotherapy, as a proxy variable for clinical effectiveness. Similarly, information on drug dosage was unavailable, and therefore, detection of underdosing, which may impact clinical effectiveness, could not be measured. Misclassification of the primary or secondary outcomes (augmentation, switch, and discontinuation) may have also occurred; however, medication dispensings are generally reliable administrative data because they require reimbursement by the health plans. We also recognize that our exploratory analysis of events suggestive of treatment intolerance and failure was limited by our reliance on algorithms using diagnosis and procedure codes and outpatient prescription drug claims submitted to insurance companies that have not been validated. As additional clinically relevant events not contained within administrative data may have occurred, it is likely that we have underestimated such events but may have also overestimated events, such as colonoscopy, that may have been used for routine surveillance. Results from a large Spanish prospective cohort study of IBD patients by Chaparro et al[25] demonstrated that 25% of patients using thiopurines experience an adverse event during treatment, with nausea being the most common event (and one which is difficult to capture in claims data). Fraser et al[13] reported similar findings of 28% of patients stopping AZA due to side effects, with nausea and vomiting as the main reason. Finally, our analysis relied upon information from commercially insured individuals and as such, patients who frequently change health plans would not have been captured, and the overall findings may not be generalizable to uninsured patients.

The primary strengths of this study were the incident user design and the broad diversity and large size of the study population. The CD cohort included initiators of 6-MP/AZA instead of prevalent users ("survivors of early 6-MP/AZA treatment") so that we could identify early noncontinuation events and patient-level characteristics associated with failure to continue 6-MP/AZA monotherapy. As shown in Figure 2, the hazard of failure to continue treatment is highest in the early months following initiation and therefore, the incident user design is appropriate and necessary in this setting.[18] Additionally, the databases utilized for this study included diverse, commercially insured individuals diagnosed with CD, ranging in age from 3 to 100 years and residing in all regions of the USA. Furthermore, the study cohort had a wide distribution of comorbidity and health care utilization, which is often lacking in RCTs. Most of the prior observational studies examining the effectiveness of 6-MP/AZA in a routine care setting were small, single-center experiences. With 3,657 individuals included in this cohort and 2,845

experiencing a noncontinuation event, the sample size was sufficiently large to examine a wide range of patient-level predictors, while allowing for broad generalizability to the commercially insured CD population in the USA.

In summary, most patients who initiate on 6-MP/AZA monotherapy for CD do not continue on this treatment beyond 1 year, suggesting the limited long-term impact of this therapeutic strategy. In contrast to some adult and the pediatric RCTs, the lower real-world clinical effectiveness of 6-MP/AZA monotherapy may be due to differences in a variety of factors, such as disease severity, patient demographics, comorbidity, adherence, and health care utilization.

Author contributions

SFC, MDK, and JLL conceived and designed the study. CFC and JKA acquired and analyzed the data. JLL, MDK and SFC interpreted the data. JLL, MDK, CFC, JKA, and SFC drafted the article or revised it critically for important intellectual content. All authors approved the final version of the manuscript.

Disclosure

Results of this study were presented at the 28th International Conference on Pharmacoepidemiology and Therapeutic Risk Management in Barcelona, Spain on August 23–26, 2012. SFC, JKA, and CFC are employees of GlaxoSmithKline. JLL and MDK are consultants to GlaxoSmithKline. As such, the study sponsor had involvement in all aspects of the study including, study design, analysis, and interpretation of data, in the writing of the manuscript, and in the decision to submit the manuscript for publication; the study sponsor did not have a role in data collection. The authors report no other conflicts of interest.

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Supporting information

Table S1 Administrative codes used to identify an initial 6-MP/AZA treatment discontinuation, switch, and augmentation

Source	Description	Codes
NDC, HCPCS	Azathioprine	49452078301 51552077902 51552077904 51927225800 00173059871 55390060020 60976059871 65483055101 65649024141 66591024141 00054408425 00054808425 00081059756 00173059755 00378100501 00406200301 00781105901 00781507501 23490511009 52959007900 54868092101 54868092104 54868531000 54868531001 54868531002 54868531004 57866902101 60976059755 65483059010 66479030110 66591022141 68084022901 68084022911 68382000301 68382000305 68462050201 65649023141 66591023141 38779031203 38779031206 49452078201 49452078203 49452078302 C9436 J7500 J7501 K0119 K0120
NDC, HCPCS	6-MP	00054458111 00054458127 00081080725 00081080765 00093551006 00173080725 00173080765 00378354725 00378354752 38779142703 38779142704 38779142706 49884092202 49884092204 51927200000 54868528200 57844052206 57844052207 57844052252 68084032521 68258910301 S0108
NDC, HCPCS	Methotrexate	49452460002 49452460003 49452460102 49452460104 51552105401 51552105409 51927156500 00205532618 63323012140 58406068318 61703040804 63323012104 66479013613 00555092901 51285036801 00555094501 51285036901 55390014301 58406067105 63323012250 66479013929 00005450704 00005450705 00005450707 00005450709 00005450723 00005450791 00054455015 00054455025 00054855003 00054855005 00054855006 00054855007 00054855010 00054855025 00182153901 00182153995 00364249901 00364249936 00378001401 00378001450

(*Continued*)

Table S1 (*Continued*)

Source	Description	Codes
		00405464301
		00405464336
		00536399801
		00536399836
		00555057202
		00555057235
		00555057245
		00555057246
		00555057247
		00555057248
		00555057249
		00603449921
		00677161001
		00781107601
		00781107636
		00904174960
		00904174973
		00904601260
		23490588900
		49999038024
		51079067001
		51079067005
		51079067086
		51079067087
		51285050902
		51432052203
		52959024400
		54569181800
		54868382600
		54868382601
		54868382602
		54868382603
		54868382604
		54868382605
		54868382606
		54868382607
		55289092430
		59911587401
		62701094036
		62701094099
		67253032010
		67253032036
		67253058042
		67253058043
		67253058044
		67253058045
		67253058046
		68115063200
		58406068312
		63323012108
		58406067301
		66479013721
		54868471600
		58406068316
		63323012110
		63323012310
		66479013619

(*Continued*)

Table S1 (*Continued*)

Source	Description	Codes
		00186142013
		00205455626
		00469288030
		10019094001
		10019094002
		10019094101
		10139006202
		10139006210
		10139006240
		53905003110
		53905003210
		53905003410
		55390003110
		55390003210
		55390003310
		55390003410
		58406068114
		58406068117
		61703035038
		61703040707
		61703040732
		61703040813
		61703040822
		61703040832
		61703040841
		61703040858
		66479013501
		66479013509
		66758004002
		66758004008
		66758004101
		00205933792
		54569452500
		54868017301
		54868479600
		58406068315
		61703040807
		63323012102
		63323012302
		66479013611
		00555092701
		51285036601
		00555092801
		51285036701
		38779003503
		38779003504
		38779003506
		38779003511
		62991120001
		62991120002
		63370015410
		63370015415
		63370015425
		J8610
		J9250
		J9260

(*Continued*)

Table S1 (*Continued*)

Source	Description	Codes
NDC, HCPCS	Natalizumab	59075073015, C9126, J2323, Q4079
NDC, HCPCS	Anti-TNFs	50474070062 50474071079 00074379902 00074433902 00074433906 00074433907 00074937402 54569552400 54868482200 57894003001 C9249 J0135 J0718 J1745 S9359

Abbreviations: NDC, National Drug Code; HCPCS, Healthcare Common Procedural Coding System; TNF, tumor necrosis factor.

Table S2 Administrative codes used to identify possible indicators of intolerance or active disease

Source	Description	Codes
ICD-9 CM	Acute pancreatitis	577.0
ICD-9 CM	Liver toxicity	570, 790.4
ICD-9 CM	Low white blood cell count	288.5, 288.0
ICD-9 CM	GI procedures	43200–43273, 44360–44397, 45300–45392, 46600–46615
NDC	Oral steroid prescription	Codes
ICD-9 CM	Crohn's disease-related hospitalization	555.0, 555.1, 555.2, 555.9

Abbreviations: NDC, National Drug Code; ICD-9 CM, International Classification of Diseases, ninth revision codes; GI, gastrointestinal.