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Stopping 5-aminosalicylates in patients with ulcerative colitis starting biologic therapy does not increase the risk of adverse clinical outcomes: analysis of two nationwide population-based cohorts

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Abstract

Objective—The benefit of continuing 5-aminosalicylate (5-ASA) in patients with ulcerative colitis (UC) who initiate anti-tumour necrosis factor-alpha (anti-TNF) biologics is unknown. We aimed to compare clinical outcomes in patients with UC already on 5-ASA who started anti-TNF and then either stopped or continued 5-ASA.

Design—Our primary outcome was any adverse clinical event defined as a composite of new corticosteroid use, UC-related hospitalisation or surgery. We used two national databases: the United States (US) Truven MarketScan health claims database and the Danish health registers. Patients with UC who started anti-TNF after having been on oral 5-ASA for at least 90 days were included. Patients were classified as stopping 5-ASA if therapy was discontinued within 90 days of starting anti-TNF. We performed multivariable Cox regression models controlling for demographics, clinical factors and healthcare utilisation. Adjusted HRs (aHR) with 95% CI are reported comparing stopping 5-ASA with continuing 5-ASA.

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J-FC and TJ contributed equally. RCU and BNL contributed equally.

Contributors RCU, TU and JFC developed the study concept. RCU, BNL, CBJ, JFC, KHA and TJ designed the study. BNL and CBJ performed data analysis. RCU, BNL, CBJ, MA, TU, JFC, KHA and TJ interpreted the analyses and contributed substantially to the manuscript. RCU and BNL drafted the first version of the manuscript.

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Results—A total of 3589 patients with UC were included (2890 US and 699 Denmark). Stopping 5-ASA after initiating anti-TNF was not associated with an increased risk of adverse clinical events in the U.S. cohort (aHR 1.04; 95% CI 0.90 to 1.21, $p=0.57$) nor in the Danish cohort (aHR 1.09; 95% CI 0.80 to 1.49, $p=0.60$). Results were similar in sensitivity analyses investigating concomitant immunomodulator use and duration of 5-ASA treatment before initiating anti-TNF.

Conclusion—In two national databases, stopping 5-ASA in patients with UC starting anti-TNF therapy did not increase the risk of adverse clinical events. These results should be validated in a prospective clinical trial.

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) that results in chronic, relapsing inflammation affecting the colon.¹ For patients with mild to moderate UC, oral and/or rectal 5-aminosalicylate (5-ASA) agents are considered first-line options for treatment.² After 8 weeks of 5-ASA treatment, clinical response and remission can occur in up to 80% and 50% of patients, respectively.³⁴ Patients who fail 5-ASA will require escalation of therapy. Biologics are currently the most effective immunosuppressive agents for the treatment of UC. In patients who are refractory to conventional treatments, anti-tumour necrosis factor-alpha (anti-TNF) biologics are effective at inducing clinical response, clinical remission and endoscopic remission.⁴ There has been a significant amount of research conducted on the impact of discontinuing immunomodulators (ie, azathioprine, 6-mercaptopurine) and biologics on clinical outcomes in IBD due to their cost and side effects.⁵ However, after a patient with UC requires escalation to biologics, the benefit of continuing or withdrawing 5-ASA is currently unknown. This is of significant interest to patients and payers as 5-ASA agents are costly and often require taking multiple pills a day. Patients who discontinue or are non-adherent to 5-ASA appear to be at increased risk of flares although this has not been specifically studied with concomitant biologic agents.⁶⁷ Further, in a subset of patients, 5-ASA may be associated with a paradoxical worsening of UC symptoms prompting some clinicians to discontinue these agents during severe flares.⁸⁹ A recent expert consensus on treatment withdrawal from the European Crohn's and Colitis Organisation recommended continuing 5-ASA in the long term in patients with UC but did not comment on whether to stop or continue 5-ASA among patients starting biologics.¹⁰ We therefore aimed to compare clinical outcomes in patients with UC already on oral 5-ASA who started an anti-TNF agent and then either continued or discontinued oral 5-ASA agents using two large nationwide population-based cohorts.

METHODS

Study populations

We used two large national databases, one from the United States (US) and the other from Denmark. The US cohort was derived from the Truven Health MarketScan Commercial Database which is the largest multipayer health claims databases in the US containing over 450 million patient-level entries per year. This database includes deidentified individual-level healthcare claims information that reflects real-world treatment patterns across the continuum of healthcare services (eg, inpatient, outpatient, pharmacy). The MarketScan data

also include enrolment data from large employers and health plans. For this study, all enrollees from 2007 through 2016 were included. The International Classification of Diseases (ICD) 9th and 10th Revision codes were used to identify patients with at least one code for UC (556.x and K51.x). Patients with history of bowel resection were excluded. Other inclusion criteria were initiation of anti-TNF biologic therapy (ie, infliximab, adalimumab or golimumab), continuation of biologic therapy for at least 90 days and use of 5-ASA for at least 90 days prior to initiation of biologic therapy. Medication prescriptions were identified using string searches of medication names.

The Danish cohort was drawn from three nationwide Danish health registers, the Danish National Patient Register (NPR), the Danish Prescription Register, and the Danish Central Personal Registration System, using a unique personal identification number for linkage. The NPR includes records on all discharges from hospitals in Denmark since 1977 and outpatient contacts since 1995. For this study, we collected information about UC diagnoses, gastrointestinal surgery, biologic therapy and hospital admissions from the NPR. Information about use of biologic therapy, 5-ASA, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) and corticosteroids was collected from the Danish Prescription Register which was established in 1995 and includes information on all prescriptions filled by Danish residents in community pharmacies in Denmark. Information about death and emigration was collected from the Danish Central Personal Registration System. Data from the registers were available through 31 December 2014. Patients with UC were identified using ICD-8 (563.19, 569.04) and ICD-10 codes (DK51). Patients with history of bowel resection were excluded. Anti-TNF biologic therapies were identified using Anatomical Therapeutic Chemical (ATC) codes (L04AB02, L04AB04, L04AB05) and procedure codes (B0HJ18A, B0HJ18A1, B0HJ18A3). 5-ASA treatments were identified using the ATC code A07EC. Inclusion criteria were identical to the US cohort. All patients with UC who initiated biologic therapy, continued for at least 90 days and were on 5-ASA for at least 90 days prior to biologic initiation were included.

Outcomes

Our primary outcome was a composite of adverse clinical events defined as need for new corticosteroid therapy, UC-related hospitalisation or surgery. The need for corticosteroid therapy was defined as a new prescription at least 90 days after the initiation of biologic therapy. Hospitalisations were defined as any admission with UC as the primary or secondary diagnosis. If UC was coded as the secondary diagnosis, the primary diagnosis had to be related to GI symptoms, such as nausea, vomiting, abdominal pain, diarrhoea, constipation or gastrointestinal bleeding. Hospitalisations were counted if the admission occurred at least 1 day after the initiation of anti-TNF therapy. Intestinal surgeries were identified in the MarketScan database by ICD-9/10 and Common Procedural Terminology (CPT) codes. These included small bowel resections (ICD: 45.6, 45.73, 45.79, 0DB8, 0DBA, 0DBB, 0DT8, 0DTA, 0DTB; CPT: 44120, 44121, 44160, 44202, 44203, 44205) and colectomies (ICD: 17.3, 45.7, 45.8, 48.4, 48.5, 0DBE–0DBH, 0DBK–0DBQ, 0DTE–0DTH, 0DTK–0DTQ; CPT: 44140–44160, 44204–44212, 45110–45123, 45395–45397). Intestinal surgeries in the NPR were identified by operation codes KJH, KJE, KJF and KJG.

Variables

Patients with UC who discontinued 5-ASA treatment within 90 days after initiation of anti-TNF therapy were classified as having discontinued 5-ASA while those who remained on 5-ASA treatment for at least 90 days after initiation of anti-TNF therapy were classified as having continued 5-ASA. Additional variables that were analysed in both cohorts included age, sex, duration of 5-ASA treatment before anti-TNF initiation and healthcare utilisation prior to initiation of biologic therapy. Baseline healthcare utilisation was assessed as a measure of UC severity prior to biologic therapy and included prior corticosteroid use (remote defined as 365 to 90 days prior to anti-TNF therapy or recent defined as within 90 days prior to anti-TNF therapy), number of hospitalisations in the year before starting anti-TNF (categorised as 0, 1–2, or more than 2) and number of emergency department visits in the year before starting anti-TNF (categorised as 0, 1, or more than 2). Data on the duration of UC were available in the NPR but not MarketScan, and were thus included as a potential confounder in analyses of the former but not the latter.

Statistical analyses

Descriptive analyses were used to evaluate the baseline characteristics of patients with UC who discontinued or continued 5-ASA. The Student's t-test was used to compare continuous variables and the X^2 test was used to compare categorical variables. The Wilcoxon rank-sum test was used to compare continuous variables with a skewed distribution. The incidence rate of events was calculated as the number of adverse clinical outcomes divided by the person-time. Cox regression and Kaplan-Meier methods were used to compare the risk of adverse clinical events between patients with UC who discontinued versus continued 5-ASA therapy. No violations of the proportional hazards assumption were identified. Outcomes were evaluated individually and as the composite primary outcome. Multivariable models were adjusted for age, sex, duration of 5-ASA treatment and healthcare utilisation (corticosteroid use, hospitalisation and emergency department visits) prior to the initiation of anti-TNF therapy. Multivariable analyses of the Danish cohort also included duration of UC diagnosis, which was not available in the MarketScan database. Adjusted HRs (aHR) and 95% CIs are reported with an aHR greater than 1 indicating an increased risk of the event in the 5-ASA discontinuation group compared with continuation. Follow-up time for the MarketScan data was limited to 3 years due to the relative lack of longitudinal follow-up data beyond that time frame. Maximum follow-up time in the Danish cohort was 9 years. Subgroup analyses evaluated the effect of concomitant immunomodulator use (prescribed within 30 days before or after initiation of biologic therapy) on the risk of adverse clinical events. Sensitivity analyses were performed using different criteria for the number of days (30, 60 and 180) on 5-ASA prior to anti-TNF therapy. We calculated that our analysis had 80% power to detect a 10% absolute difference in the composite primary outcome. Statistical significance was defined as a two-sided alpha of less than 0.05. Statistical analyses were performed using SAS V9.4, Stata SE V14.2 (College Station, Texas) and Stata MP V15.1 (College Station, Texas).

Ethics

The study protocol related to the use of the MarketScan data was reviewed and deemed exempt by the Institutional Review Board of Stanford University. An access and linkage permission was obtained from the Danish Data Protection Agency (J number 2008–54-0472) for the Danish cohort. Research based on pre-existing, routinely collected data does not require ethical permission in Denmark.

RESULTS

Baseline patient characteristics

The US and Danish cohorts had 2890 and 699 patients with UC, respectively, who met inclusion criteria (table 1). In the US cohort, there were 939 (32.5%) patients who discontinued 5-ASA and 1951 (67.5%) patients who continued 5-ASA after initiation of anti-TNF therapy. Those who discontinued 5-ASA were slightly younger than those who continued 5-ASA (40.6 vs 41.7, $p=0.04$). Prior to anti-TNF therapy, those who discontinued 5-ASA had a shorter duration on 5-ASA treatment (median 305 vs 495 days, $p<0.01$), more emergency department visits (35.4% vs 31.2% with one or more visits over the past year, $p=0.046$) and lower prevalence of immunomodulator use (31.0% vs 36.8%, $p<0.01$). There was otherwise no difference in sex, pre-biologic corticosteroid use or hospitalisations between the groups. Median follow-up time after initiation of biologic therapy was similar between the groups.

In the Danish cohort, there were 225 (32.2%) patients who discontinued 5-ASA and 474 (67.8%) patients who continued 5-ASA after initiation of anti-TNF therapy (table 1). The ages at initiation of biologic therapy and at time of UC diagnosis were similar between both groups. However, the pre-biologic disease duration was shorter in those who discontinued 5-ASA (median 3.2 years vs 4.1 years, $p=0.04$). Those who discontinued 5-ASA had a significantly shorter duration of pre-biologic 5-ASA treatment (median 296 vs 861 days, $p<0.01$). There was otherwise no difference in sex, baseline healthcare utilisation or immunomodulator use between the groups. The follow-up time was shorter in those who discontinued 5-ASA (median 155 vs 196 days, $p<0.01$).

Adverse clinical events

In univariable analysis, discontinuation of 5-ASA in patients with UC starting anti-TNF was not associated with an increase in adverse clinical events compared with continuing 5-ASA in both the US and Danish cohorts. The proportion of patients experiencing the primary endpoint (composite of need for new corticosteroid therapy, UC-related hospitalisation or surgery) over time was not significantly different in both cohorts (figures 1 and 2). In addition, no significant differences were seen when analysing the individual components of the composite primary outcome (figures 1 and 2). One exception was an increased risk of hospitalisation among patients with UC who discontinued 5-ASA in the Danish cohort (log-rank $p=0.04$, figure 2B). After adjusting for age, sex, duration of prebiologic 5-ASA treatment, UC disease duration (Danish cohort only) and baseline healthcare utilisation in multivariable analysis, no significant differences were seen in the primary outcome in both the US and Danish cohorts when comparing patients with UC who discontinued with those

who continued 5-ASA after initiating anti-TNF therapy (table 2). The risk of the individual clinical events that constituted the primary outcome was also similar between the 5-ASA continuation and discontinuation groups in both cohorts with no significant differences observed in adjusted analyses (table 2).

We conducted additional analyses to further examine the association of 5-ASA discontinuation with adverse clinical outcomes. When stratifying patients with UC by concomitant immunomodulator use at time of anti-TNF initiation, there was no increased risk of the primary endpoint (composite of adverse clinical events) following discontinuation of 5-ASA regardless of whether patient was on monotherapy or combination therapy (table 3). There was also no significant difference in the risk of corticosteroid use or hospitalisation with discontinuation of 5-ASA in either cohort. 5-ASA discontinuation did not impact risk of surgery in the Danish cohort and in US patients on combination therapy. However, in the US cohort, discontinuation of 5-ASA in patients initiating biologic monotherapy was associated with a lower risk of surgery (aHR 0.26, 95% CI 0.10 to 0.66, $p < 0.01$). We also examined adjusted Cox regression models for the primary outcome and individual component outcomes requiring differing times on 5-ASA prior to anti-TNF initiation (30, 60 and 180 days). No significant differences were observed for any of the outcomes with differing times on 5-ASA prior to discontinuation (online supplementary tables 1–3).

DISCUSSION

In this study of two large national databases, we observed that discontinuation of 5-ASA after initiation of anti-TNF therapy in patients with UC did not increase the risk of adverse clinical outcomes, including corticosteroid use, hospitalisation and surgery. These findings held after controlling for potential confounders and baseline healthcare utilisation. Importantly, results were consistent across two independent cohorts from different countries. This observation is clinically relevant as there are currently no published data on whether patients with UC who initiate anti-TNF therapy can safely discontinue 5-ASA therapy. To our knowledge, no prior publications have examined the impact of stopping 5-ASA treatment in patients requiring escalation to anti-TNF therapy. Given the potential benefits of discontinuing 5-ASA drugs, including decreased costs, reduced risk of medication side effects (although rare) and less polypharmacy, our study is the first to provide data supporting 5-ASA discontinuation after escalation to anti-TNF. However, clinical trials are needed to further establish this as a preferred medication de-escalation strategy in UC.

Our study provides new information on the often-encountered clinical scenario of patients with UC already on 5-ASA who then require escalation of therapy. Prior literature investigating the impact of 5-ASA discontinuation in UC is limited. Previous studies have been on adherence or discontinuation in patients already in remission. A prospective cohort of patients with UC in remission on 5-ASA found that patients who were not adherent to their medication had more than a fivefold increased risk of flare, defined by recurrence of symptoms, compared with adherent patients.¹¹ An analysis of health insurance claims data found that patients with UC who were non-adherent to 5-ASA, defined as a medication to possession ratio less than 0.8, were significantly more likely to be hospitalised over a 12-month follow-up period.¹² One clinical trial examined the impact of 5-ASA continuation on

patients with UC who were in clinical, endoscopic and histological remission for at least 1 year on mesalamine or sulfasalazine and found that patients randomised to placebo were significantly more likely to have a relapse over 12 months compared with those randomised to mesalamine.⁶ A retrospective study, published in abstract form only, similarly found that over half of patients with UC in remission on 5-ASA who withdrew maintenance 5-ASA experienced a new flare within a median of 27 months.¹³ These studies suggest that 5-ASA discontinuation or non-adherence increases the risk of adverse clinical outcomes but did not address the impact in the setting of concomitant immunosuppressant treatment. One prior retrospective study did investigate the effect of 5-ASA treatment in patients with IBD with clinically quiescent disease on azathioprine and found no benefit to concomitant 5-ASA in maintaining remission.¹⁴ A recent study pooling anti-TNF clinical trial data examined if concomitant 5-ASA treatment at the start of the trial improved outcomes but found no difference among patients on or off 5-ASA.¹⁵ This is a related question to our study but is distinct from examining the impact of stopping 5-ASA among patients who were previously on treatment with these agents. Our results suggest that continuation of previously prescribed 5-ASA does not provide benefit after escalation to more potent anti-TNF biologic medications. We suspect that this is most likely because the anti-inflammatory effects of anti-TNF alone (or in combination with an immunomodulator) are more than sufficient for controlling UC with no additive or synergistic effect from co-treatment with 5-ASA, likely reflecting the higher potency of biologic agents. Another potential explanation for our observation is that dominant molecular pathways in moderate to severe UC are more directly targeted by anti-TNF as opposed to 5-ASA treatments.

Since clinical trial evidence supports improved outcomes with combination therapy in UC, we explored if concomitant immunomodulator therapy may modify risk of adverse events after 5-ASA discontinuation.¹⁶ In addition, some prior studies have suggested that 5-ASA interacts with immunomodulator metabolism and can increase 6-thioguanine levels.^{17–19} The presence or absence of concomitant immunomodulators did not generally modify the risk of major adverse outcomes when discontinuing 5-ASA. In the US cohort, there was an apparent reduction in risk of intestinal surgery when discontinuing 5-ASA in patients who initiate biologic monotherapy. This finding was not seen in the Danish cohort. This statistically significant finding in the US cohort may be explained by an artefactual effect of the low incidence of intestinal surgeries, where the relative (proportional) difference is great, but the absolute difference is very low (1.0 per 100 person-years).

This study has several strengths. First, the study included two completely independent population cohorts that permitted cross-validation of results. Although we present the results within the same study, the cohorts were analysed separately by two separate statisticians to minimise risk of bias. The rigour of this approach and the consistency in the results from two different countries provide greater confidence in the validity of the findings. Second, the use of large population-based cohorts provided the ability to select many patients in the specific clinical scenario of interest as well as improve the precision and power of effect estimates. This is particularly important given our null findings when comparing the discontinuation and continuation of 5-ASA. Third, the source data were derived from national research infrastructures that have well-characterised population databases with robust longitudinal follow-up and complete medication histories. Given the longer term

follow-up of patients in these cohorts we were able to observe the progression of medical history over time and capture potential short and long-term adverse outcomes following discontinuation of 5-ASA.

We acknowledge several limitations of this study. First, we used databases that relied on administrative health claims to define patient characteristics and outcome. There is therefore the potential for misclassification from improper coding of diagnoses and we had to rely on prescriptions as a measure of patients actually taking medications. However, findings were consistent in both databases and inclusion criteria required UC-specific medications so misclassification was likely low. The Danish cohort has been validated and demonstrated at least 90% validity of UC diagnoses comparing charts with diagnosis codes.²⁰ The US database has unfortunately not had similar validation of case definitions but our definition was strict based on ICD-9 code and two UC-related medication codes (5-ASA and anti-TNF) so misclassification of cases should likely be low. Second, both cohorts lack granular UC-specific data, such as clinical symptoms, laboratory values, disease extent by Montreal classification, smoking status and endoscopic findings that would allow for more detailed control of disease severity. We controlled for markers of disease severity prior to 5-ASA discontinuation and all patients required escalation to anti-TNF therapy so disease severity should be balanced between groups. If disease severity was not comparable between those who stopped or continued 5-ASA we would expect to see significant differences in risk of adverse events which was not observed. Third, given the retrospective nature of this study, there may have been unmeasured confounders that contributed to the decision about continuing 5-ASA in some patients, which could have attenuated risk of major adverse outcomes. However, given variability in practice patterns with the management of UC and the lack of consensus on when to discontinue 5-ASA, it is highly unlikely that clinicians would have employed similar algorithms for discontinuing or continuing 5-ASA. Since our study examined to different countries, the US and Denmark, clinical practice patterns in each cohort were likely heterogeneous given differing medical systems and similar outcomes were still observed. Consequently, it is highly unlikely that any one unmeasured confounder would have significantly biased the results.

In addition, we did not include stopping anti-TNF as an endpoint due to insufficient data on reason for discontinuation. Using anti-TNF discontinuation as an endpoint may have misclassified patients as treatment failures when the biologic was stopped for reasons other than failure to improve their UC (e.g. side effects, cost, non-adherence). In fact, a study from Denmark found that the most common reason for infliximab discontinuation in UC was remission so this would have been an inappropriate endpoint given our aims.²¹ An important consideration with any longitudinal database study is immortal time bias. Immortal time is the span of follow-up in which the outcome of interest could not occur due to the exposure definition. We think the potential impact of this is likely limited in our study. Exposure was defined as stopping 5-ASA within 90 days of starting anti-TNF and the definition of starting anti-TNF treatment was restricted to at least 90 days of anti-TNF before the start of follow-up. Therefore, the exposure (5-ASA stop or continue) was determined during the initial 90 days in which patients were required to be on anti-TNF before inclusion in the cohort. Outcomes of interest for our analysis could not have occurred during this initial 90-day anti-TNF treatment period in both groups (stop and continue 5-ASA). However, we do not

capture very early events after starting anti-TNF (within 90 days of starting). We suspect that these patients are a specific sicker subpopulation in which the question of impact of 5-ASA discontinuation is of less clinical relevance.

A key issue that we were unable to fully evaluate is that 5-ASA may be continued longer term because of its potential benefit as a preventive agent against dysplasia and colorectal cancer. We were unable to assess this given a very low number of events of advanced colorectal neoplasia in both cohorts (fewer than five diagnoses of colorectal cancer) which precluded meaningful analysis. However, rates of colorectal cancer in IBD have significantly decreased in recent decades at the same time immunosuppressant use increased and data are conflicting on the impact of 5-ASA as a chemopreventive agent.^{22–24} Further studies are needed to help delineate the relative contribution of different IBD medications to decreasing rates of colon cancer.

In conclusion, using two population-based databases, we observed that discontinuation of 5-ASA after initiating anti-TNF therapy in UC was not associated with an increased risk of major adverse clinical outcomes. Our findings suggest that patients with UC can safely discontinue 5-ASA after escalating therapy to an anti-TNF. Prospective studies investigating the benefits and risks of 5-ASA discontinuation after biologic initiation are needed to confirm our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing interests RCU has served as an advisory board member or consultant for Janssen, Pfizer and Takeda; research grant from AbbVie. JFC has served as an advisory board member or consultant for AbbVie, Amgen, Boehringer-Ingelheim, Arena Pharmaceuticals, Celgene, Celltrion, Enterome, Eli Lilly, Ferring Pharmaceuticals, Genentech, Janssen and Janssen, Medimmune, Merck & Co, Nextbiotix, Novartis Pharmaceuticals, Otsuka Pharmaceutical Development & Commercialization, Pfizer, Protagonist, Second Genome, Gilead, Seres Therapeutics, Shire, Takeda, Theradiag; speaker for AbbVie, Ferring, Takeda, Celgene; stock options: intestinal Biotech Development, Genfit; research grants: AbbVie, Takeda, Janssen and Janssen.

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Significance of this study

What is already known on this subject?

- 5-Aminosalicylate (5-ASA) medications are first-line therapies for mild to moderate ulcerative colitis (UC).
- Discontinuation of or non-adherence to 5-ASA appears to increase the risk of having a disease flare in patients with UC.
- It is unknown if there is benefit to continuing 5-ASA in patients with UC who require escalation of therapy to anti-tumour necrosis factor-alpha (anti-TNF) agents.

What are the new findings?

- In two population-based databases, patients with UC on 5-ASA for at least 90 days and started on anti-TNF who then discontinued 5-ASA medications did not have an increased rate of adverse clinical events (new corticosteroid use, hospitalisation or surgery) over time.
- After adjusting for potential confounders, there was no significant difference in the risk of adverse clinical events when comparing patients with UC who discontinued or continued 5-ASA after initiation of anti-TNF.

How might it impact on clinical practice in the foreseeable future?

- Patients with UC treated with 5-ASA who then require escalation to anti-TNF may be able to safely discontinue 5-ASA medications.

Figure 1.

Proportion of patients with UC with adverse clinical events comparing those who continued or stopped 5-ASA in US cohort. (A) Kaplan-Meier curve for needing new steroid prescription. (B) Kaplan-Meier curve for IBD-related hospitalisation. (C) Kaplan-Meier curve for surgery. (D) Kaplan-Meier curve for composite outcome (new steroid prescription, IBD-related hospitalisation and/or surgery). 5-ASA, 5-aminosalicylate; anti-TNF, anti-tumour necrosis factor- α .

Figure 2.

Proportion of patients with UC with adverse clinical events comparing those who continued or stopped 5-ASA in Danish cohort. (A) Kaplan-Meier curve for needing new steroid prescription. (B) Kaplan-Meier curve for IBD-related hospitalisation. (C) Kaplan-Meier curve for surgery. (D) Kaplan-Meier curve for composite outcome (new steroid prescription, IBD-related hospitalisation and/or surgery). 5-ASA, 5-aminosalicylate; anti-TNF, anti-tumour necrosis factor-alpha.

Table 1

Baseline patient characteristics

Characteristic	US cohort		Denmark cohort		
	Continue 5-ASA (n=1951)	Stop 5-ASA (n=939)	P values	Continue 5-ASA (n=474)	Stop 5-ASA (n=225)
Age at start of biologic therapy, mean years (SD)	41.7 (13.9)	40.6 (14.0)	0.04	41.2 (14.8)	39.3 (14.6)
Age at UC diagnosis, mean years (SD)	NA	NA		34.6 (13.9)	33.4 (13.6)
Sex			0.40		
Male	1026 (52.6)	478 (50.9)		234 (49.4)	108 (48.0)
Female	925 (47.4)	461 (49.1)		240 (50.6)	117 (52.0)
Year of initiation of anti-TNF therapy, n (%)			<0.01		
2007–2010	476 (24.4)	182 (19.4)		NA	NA
2011–2013	675 (34.6)	294 (31.3)		NA	NA
2014–2016	800 (41.0)	463 (49.3)		NA	NA
Year of initiation of anti-TNF therapy, n (%)					0.8
2003–2008	NA	NA		77 (16.2)	35 (15.6)
2009–2010	NA	NA		111 (23.4)	47 (20.9)
2011–2012	NA	NA		116 (24.5)	62 (27.6)
2013–2014	NA	NA		170 (35.9)	81 (36.0)
Pre-anti-TNF disease duration, median years (P25, P75)	NA	NA		4.1 (1.3, 10.2)	3.2 (1.1, 8.3)
Pre-anti-TNF 5-ASA treatment, median days (P25, P75)	495 (404, 633)	305 (211, 363)	<0.01	861 (526, 1566)	296 (183, 583)
Pre-anti-TNF corticosteroid use, n (%)			0.20		0.06
None	538 (27.6)	260 (27.7)		55 (11.6)	33 (14.7)
Remote	675 (34.6)	296 (31.5)		130 (27.4)	44 (19.6)
Recent (< 90days)	738 (37.8)	383 (40.8)		289 (61.0)	148 (65.8)
Pre-anti-TNF hospitalisations, n (%) *			0.09		0.4
0	1510 (77.4)	707 (75.3)		222 (46.8)	97 (43.1)
1–2	394 (20.2)	217 (23.1)		194 (40.9)	93 (41.3)
>2	47 (2.4)	15 (1.6)		58 (12.2)	35 (15.6)
Pre-anti-TNF emergency department visits, n (%) *			<0.05		0.9
0	1343 (68.8)	606 (64.5)		403 (85.0)	191 (84.9)
1–2	560 (28.7)	312 (33.2)		53 (11.2)	24 (10.7)

Characteristic	US cohort			Denmark cohort		
	Continue 5-ASA (n=1951)	Stop 5-ASA (n=939)	P values	Continue 5-ASA (n=474)	Stop 5-ASA (n=225)	P values
>2	48 (2.5)	21 (2.2)		18 (3.8)	10 (4.4)	
Immunomodulator use $\pm$ 30 days from initiation of anti-TNF therapy, n (%)			<0.01			0.3
No	1233 (63.2)	648 (69.0)		305 (64.4)	135 (60.0)	
Yes	718 (36.8)	291 (31.0)		169 (35.7)	90 (40.0)	
Follow-up time from initiation of anti-TNF therapy, median days (P25, P75) [†]	287 (155, 568)	271 (160, 524)	0.16	196 (99, 420)	155 (88, 297)	<0.01

* Within 365 days prior to initiation of biologic therapy.

[†] Defined as the time from initiation of biologic therapy until the end of biologic therapy, loss of follow-up or administrative censoring.

5-ASA, 5-aminosalicylate; NA, not applicable; P25, 25th percentile; P75, 75th percentile; anti-TNF, anti-tumour necrosis factor-alpha.

Table 2

Risk of adverse clinical events comparing patients who continue or discontinue 5-ASA therapy after initiating anti-TNF therapy

	Continue 5-ASA		Discontinue 5-ASA		Discontinue versus continue 5-ASA	
	IR (95% CI), per 100 person-years		IR (95% CI), per 100 person-years		aHR (95% CI)*	P values
US cohort						
New steroid use	32.9 (30.3 to 35.7)		37.8 (33.7 to 42.4)		1.04 (0.88 to 1.23)	0.67
Hospitalisation	14.2 (12.6 to 16.0)		15.1 (23.8 to 17.9)		0.97 (0.76 to 1.23)	0.81
Surgery	2.5 (1.9 to 3.3)		2.0 (1.3 to 3.1)		0.70 (0.38 to 1.26)	0.24
Composite	44.7 (41.6 to 48.1)		51.2 (46.2 to 56.7)		1.04 (0.90 to 1.21)	0.57
Denmark cohort						
New steroid use	23.9 (19.8 to 28.9)		22.7 (16.8 to 30.6)		1.05 (0.71 to 1.55)	0.8
Hospitalisation	13.0 (10.2 to 16.6)		22.2 (16.4 to 30.1)		1.35 (0.88 to 2.08)	0.2
Surgery	6.2 (4.4 to 8.7)		10.2 (6.7 to 15.5)		1.36 (0.75 to 2.46)	0.3
Composite	39.0 (33.4 to 45.6)		43.7 (34.6 to 55.2)		1.09 (0.80 to 1.49)	0.6

* In the US cohort, models were adjusted for age, sex, duration of pre-biologic 5-aminosalicylate treatment and baseline healthcare utilisation (hospitalisation, emergency department visits, corticosteroid use, GI surgery). In the Danish cohort, models were adjusted for age, sex, duration of UC at initiation of biologic therapy, duration of pre-biologic 5-aminosalicylate treatment and baseline healthcare utilisation (hospitalisation, emergency department visits, corticosteroid use, GI surgery).

5-ASA, 5-aminosalicylate; aHR, adjusted HR; IR, incidence rate; anti-TNF, anti-tumour necrosis factor-alpha.

Table 3

Risk of adverse clinical events comparing patients who discontinue 5-ASA with those who continue 5-ASA therapy, stratified by concomitant use of immunomodulator therapy

	<u>Biologic without immunomodulator</u>		<u>Biologic with immunomodulator</u>	<u>P values</u>
	aHR (95% CI)*	P values	aHR (95% CI)*	
US cohort				
Steroid	0.99 (0.80 to 1.22)	0.94	1.14 (0.86 to 1.53)	0.36
Hospitalisation	0.80 (0.59 to 1.09)	0.17	1.35 (0.91 to 2.01)	0.14
Surgery	0.24 (0.09 to 0.62)	<0.01	1.70 (0.76 to 3.78)	0.19
Composite	0.96 (0.80 to 1.16)	0.69	1.22 (0.95 to 1.57)	0.11
Denmark cohort				
Steroid	1.15 (0.72 to 1.82)	0.6	0.72 (0.34 to 1.54)	0.4
Hospitalisation	1.18 (0.69 to 2.04)	0.5	1.44 (0.69 to 3.00)	0.3
Surgery	1.33 (0.65 to 2.69)	0.4	1.19 (0.34 to 4.18)	0.8
Composite	1.13 (0.78 to 1.66)	0.5	0.92 (0.52 to 1.60)	0.8

* In the US cohort, models were adjusted for age, sex, duration of pre-biologic 5-aminosalicylate treatment and baseline healthcare utilisation (hospitalisation, emergency department visits, corticosteroid use, GI surgery). In the Danish cohort, models were adjusted for age, sex, duration of UC at initiation of biologic therapy, duration of pre-biologic 5-aminosalicylate treatment and baseline healthcare utilisation (hospitalisation, emergency department visits, corticosteroid use, GI surgery).

5-ASA, 5-aminosalicylate; aHR, adjusted HR.