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ORIGINAL RESEARCH ARTICLE

A Longitudinal Post-authorization Safety Study of Golimumab in Treatment of Ulcerative Colitis: A Cohort Study in Denmark and Sweden, 2013–2021

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Abstract

Background When golimumab (GLM) was approved for the treatment of moderate to severe ulcerative colitis (UC) in 2013, a post-authorization safety study was conducted.

Objective Our objective was to examine whether exposure to GLM was associated with an increased incidence of all-cause total colectomy, colorectal cancer, and hepatosplenic T-cell lymphoma in Denmark and Sweden.

Methods We conducted a new-user, active comparator cohort study of patients with UC in 2013–2021. Exposure to GLM, other anti-tumor necrosis factor (TNF) agents (infliximab and adalimumab) and thiopurines was a time-varying variable. Therapies were based on prescription redemptions and hospital-based administration of medications from national prescription and hospital registers. The association between exposure to study therapies and outcomes was evaluated using Poisson regression of incidence rates (IRs), presented as IR ratios (IRRs) and 95% confidence intervals (CIs).

Results A total of 5177 and 7469 patients were included in Denmark and Sweden, respectively. The IR of all-cause total colectomy per 1000 person-years was higher in Denmark (IR 42.6; 95% CI 38.9–46.2) than in Sweden (IR 16.1; 95% CI 14.2–18.0). No significant difference was observed in all-cause total colectomy between GLM and other anti-TNF agents (Denmark: adjusted IRR [aIRR] 1.28; 95% CI 0.98–1.66; Sweden: aIRR 1.17; 95% CI 0.72–1.90). A significant difference was observed between GLM and thiopurines (Denmark: aIRR 13.62; 95% CI 8.73–21.26; Sweden: aIRR 4.52; 2.75–7.41). Privacy regulations prevented analysis of a few colorectal cancer events. No hepatosplenic T-cell lymphoma events were identified.

Conclusion The IR of all-cause total colectomy with GLM was similar to that with other anti-TNF agents but was much higher than with thiopurines, probably related to confounding by indication.

1 Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that affects the colon and rectum and can be diagnosed at all ages [1]. The highest incidence of UC is reported in North America and Northern Europe. The annual incidence of UC was 18–28 per 100,000 individuals in Denmark and Sweden in 2010–2016 [2, 3].

Anti-tumor necrosis factor (TNF) therapies are recommended in UC refractory to conventional immunosuppressive treatment with 5-aminosalicylic acid, steroids and thiopurines (TP) [4]. Anti-TNF agents such as infliximab (IFX), adalimumab (ADA), and golimumab (GLM) are established therapies for the treatment of UC after failure of conventional immunosuppressive therapies [5]. IFX was the first biologic therapy approved for UC treatment [6, 7]. On September 19, 2013, GLM received the authorization from the European Medicines Agency (EMA) for the treatment of moderate to severe UC. Since TNFα mediates inflammation and modulates cellular immune responses, the possibility exists for anti-TNFα agents, including GLM, to cause immune suppression and thereby affect host defenses against infections and malignancies. Neither the pivotal registration trials nor any of the other clinical trials in the development program for GLM had suggested an association between the drug and a modified risk of colorectal cancer (CRC), dysplasia, hepatosplenic T-cell lymphoma (HSTCL), or colectomy. In connection with the authorization, a safety study

Key Points

In this post-authorization safety study in Denmark and Sweden, golimumab-exposed periods were not associated with an increased incidence rate of all-cause total colectomy compared with other anti-tumor necrosis factor therapies (adalimumab and infliximab).

An increased incidence rate of all-cause total colectomy was seen during golimumab-exposed periods compared with thiopurine-exposed periods, probably because of confounding by indication.

Privacy regulations prevented analysis of a few colorectal cancer events. No events of hepatosplenic T-cell lymphoma were presented.

was conducted to evaluate whether treatment with GLM was associated with an increased incidence of all-cause total colectomy, CRC, and HSTCL. We present key results from a post-authorization safety study requested by the EMA (EU PAS number: 11484, protocol reference number: MK-8259-013 and subsequent amendment).

Treatment failure may result in the need for total colectomy and is therefore a relevant proxy for the efficacy of medical treatment. Other and less frequent indications for colectomy are patient preference, serious adverse events due to medical treatment, colonic epithelial dysplasia, or CRC [8].

The 10-year cumulative risk of colectomy is 9–28% [9, 10], and the greatest risk is in the first 2 years after UC diagnosis [11]. Historically, up to one-quarter of patients may undergo colectomy within the first 20 years of disease, although the rate of colectomy is likely declining [8]. Patients diagnosed with UC have an increased risk of CRC [12], with an overall estimated incidence rate (IR) of 1.3 per 100,000 person-years (PYs) in Denmark and Sweden [13]. In addition to CRC, patients with UC may also have an increased risk of HSTCL, a rare lymphoma. In a study of children and adults with UC or Crohn's disease (CD) from the USA, the estimated IR was 0.3 per 1,000,000 PYs [14].

In a post-hoc analysis of the GLM PURSUIT-M and PURSUIT-LTE studies of patients with moderate to severe UC receiving long-term GLM treatment, 4.9% experienced colectomy within 4 years [15]. Only a few studies have compared the risk of colectomy between the different anti-TNF therapies, and data on GLM exposure are scarce [16, 17]. Comparing GLM and ADA in patients with UC, no difference was seen in the risk of colectomy between the treatments in a retrospective chart review study in adult patients diagnosed with UC using data from 16 national health service sites in the UK. Overall, 8.2% of the patients underwent colectomy [16].

The aim of this study was to examine whether exposure to GLM was associated with an increased incidence of all-cause total colectomy, CRC, and HSTCL in patients with moderate to severe UC in Denmark and Sweden.

2 Material and Methods

We conducted a nationwide, register-based study in Denmark and Sweden. All procedures (e.g., application of data, data management, and data analyses) were performed separately in Denmark (by AKE) and Sweden (by AG). Individual-level population-based data were extracted in both countries from the national population registers [18, 19], national patient registers [20, 21], and national prescription registers [22, 23]. Diagnoses are registered in the national patient registers using the International Statistical Classification of Diseases and Related Health Problems (ICD) versions 8, 9, and 10 codes. The national patient registers included inpatients from 1977 and 1987 in Denmark and Sweden, respectively. The Danish and Swedish registers have also included outpatient contacts from 1995 and 2001, respectively. Procedures are registered in the national patient registers using the Nordic Classification of Surgical Procedures codes (NOMESCO). Prescriptions filled at community pharmacies are registered in the national prescription registers using the Anatomical Therapeutic Classification codes. Drugs administered by hospitals are registered in the national patient registers. The codes used in this study are shown in Table 1 in the electronic supplementary material (ESM).

Individual-level linkage of data was possible because a unique personal identification code is assigned to all residents in each of the Nordic countries at birth or immigration and used as a registration key in all registers [24–26].

2.1 Study Design and Study Population

A new-user, active comparator cohort study design was used. The enrollment period was September 19, 2013, to September 18, 2020. The end of the study period was September 18, 2021, in Denmark and December 31, 2020, in Sweden. The enrollment period began on the date of EMA authorization for GLM in UC.

The study population comprised individuals with a primary diagnosis of UC in the national patient registers in the period from establishment of the patient registers (1977 in Denmark and 1987 in Sweden) until September 18, 2020. No age restriction was applied. Patients had to be naïve to the study therapy at inclusion but might have had a history of treatment with other therapies (e.g., a patient included with

GLM should be naïve to GLM at date of inclusion but could have a history of other study therapies at inclusion). Patients enrolled for TP treatment should be naïve to all anti-TNF treatments at date of inclusion. Patients were excluded if they had a history of any of the outcomes under study (partial or total colectomy, CRC, or HSTCL) or had been previously treated with etanercept or certolizumab pegol. Date of inclusion in the study was defined as date of treatment with the first study therapy during the enrollment period.

The reported positive predictive value (PPV) of UC diagnosis is 82% (95% confidence interval [CI] 81–83) in the Danish National Patient Register with one registered diagnosis [27] and 75% (95% CI 64–85) with one registered diagnosis in the Swedish National Patient Register [28].

2.2 Exposure

Exposure to GLM, other anti-TNF, and TP was a time-varying variable. As patients switch between study therapies, they could repeatedly contribute risk time to different therapies and to overlap between therapies. Therapies were defined based on prescription redemptions recorded in the national prescription registers, supplemented with hospital-based administration of medications recorded in the national patient registers. Treatment episodes were constructed based on date of initiation of each treatment, days' supply for the study therapies, switches between treatment, and periods with overlap between study therapies as described in the following and illustrated graphically in Figs. 1 and 2. We derived time at risk for all-cause total colectomy based on the constructed treatment episodes. For CRC and HSTCL outcomes, patients were assumed to be exposed forever after having commenced therapy.

Days' supply was calculated based on information on defined daily dose for prescription redemptions when available and on expert opinion for other prescription redemptions when unavailable. For treatments recorded in the national patient registers, neither amount nor duration of treatment were available. In these cases, days' supply for a registered treatment was defined based on expert opinion. Days' supply was defined as 50 days for azathioprine, 90 days for mercaptopurine, 90 days for ADA, 56 days for IFX, and 90 days for GLM.

Time at risk for all-cause total colectomy started the day after the registered start of the therapies. Time at risk was calculated as days' supply plus a 30-day grace period (presumed drug-exposed period). In addition, a 90-day extended risk period was applied (Fig. 1a, b).

A subsequent registration with the same therapy before the end of the extended risk period was considered to represent continuous periods of use (Fig. 1c–e).

Initiation of a new therapy (i.e., switch of therapy) during the period with days' supply of the previous therapy, its grace period or the extended risk period, resulted in periods with overlapping exposure between therapies (Fig. 2b–d). If the new therapy was initiated during the period with days' supply or during the grace period of the previous therapy, a 90-day overlap period between the current and new therapies was defined 1 day after initiation of the new therapy. If the new therapy was initiated during the extended risk period, the overlap period was defined as days left in the extended risk period.

For patients starting with a TP therapy as the first treatment who switched to GLM or other anti-TNF, the risk time for TP stopped at the date of switch to GLM or other anti-TNF. The risk time after switch was assigned to GLM or other anti-TNF. In case of a switch from GLM or other anti-TNF to TP, no risk time was attributed to TP.

2.3 Outcomes

The primary study outcomes were incident all-cause total colectomy and CRC. Incident HSTCL was an exploratory outcome.

All three outcomes were defined using primary ICD and surgery codes in the national patient registers. Date of diagnosis was defined as date of first admission for CRC and HSTCL. For all-cause total colectomy, the date of surgery was the date when the surgery code was used for the first time.

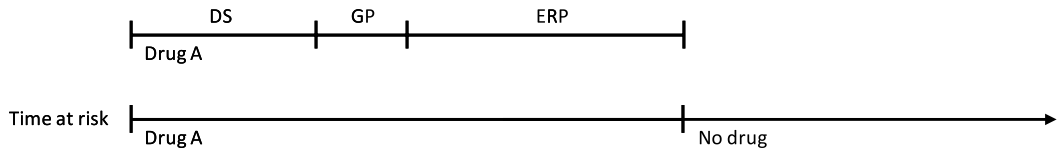
If there were too few events in one or more of the exposure groups, exposure groups were combined, for example, GLM monotherapy and GLM overlapping with other anti-TNF.

The validity of all-cause total colectomy surgery procedure codes is considered high. In Denmark and Sweden, the PPVs in the national patient registers were 97% (95% CI 93–99) and 81% (95% CI 73–87), respectively [29, 30].

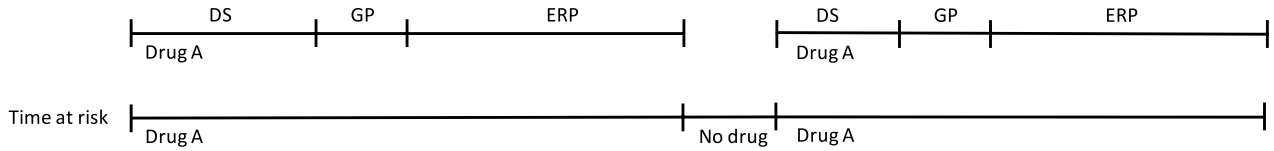
2.4 Confounders and Other Covariates in the Analysis of All-Cause Total Colectomy

To limit the risk of overadjustment, confounders were selected using the directed acyclic graphs (DAG) approach [31–34]. Potential confounders were identified through a literature review and in consultation with clinical experts (VA, EH, JL, NQ). In a DAG workshop, all potential confounders identified in the literature or suggested by the experts were illustrated in a diagram using the software DAGitty [32, 33]. Links between all variables were discussed and identified with the clinical experts. We identified the minimal sufficient adjustment set of potential confounders to include in the analysis to obtain unbiased estimates of the associations. The minimal sufficient adjustment set for the comparative analysis of GLM with other anti-TNF included age, disease duration, disease severity measured by Mayo

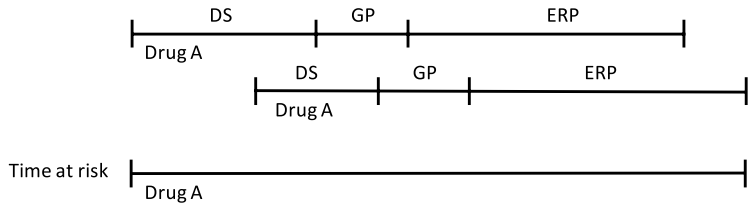
a) One treatment episode



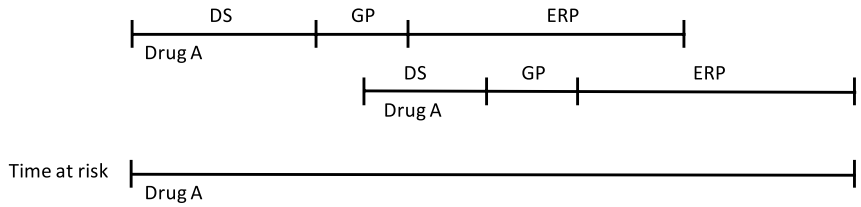
b) Two treatment episodes with the same drug, no overlap



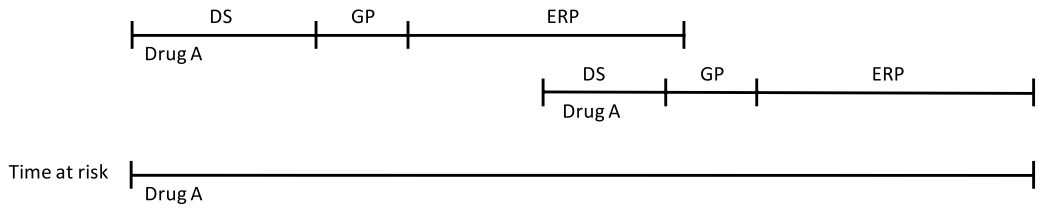
c) Two adjacent treatment episodes with the same drug, second treatment initiated during days' supply of the first treatment



d) Two adjacent treatment episodes with the same drug, second treatment initiated during grace period of the first treatment



e) Two adjacent treatment episodes with the same drug, second treatment initiated during extended risk period of first treament



◂**Fig. 1** Illustrations of the construction of treatment episodes and definition of time at risk for all-cause total colectomy for monotherapies with golimumab, other anti-tumor necrosis factor agent and thiopurines. The time at risk is calculated based on days' supply (DS), a 30-day grace period (GP), and a 90-day extended risk period (ERP)

score, calendar year, extent of UC, race/ethnicity, response to IFX, and history of primary sclerosing cholangitis, dysplasia, therapy with steroids, and therapy with biologics (Figure 1 in the ESM). The minimal sufficient adjustment set for the comparative analysis of GLM with TP included age, disease duration, disease severity measured by Mayo score, calendar year, extent of UC, race/ethnicity, response to IFX, and history of dysplasia, therapy with steroids, and primary sclerosing cholangitis (Figure 1 in the ESM). However, information on response to IFX, race/ethnicity, disease severity measured by Mayo score, and history of dysplasia was not available and therefore was not included in the final DAG models.

An additional set of covariates was described in the study protocol and in the statistical analysis plan. These pre-specified covariates adjusted for in the comparative analysis of GLM with other anti-TNF included sex, age, disease duration, calendar year, extent of UC, and history of lower endoscopies, therapy with steroids, primary sclerosing cholangitis, arthropathies, psoriasis, CD, therapy with TP, and therapy with biologics. Similarly, in accordance with the protocol, the pre-specified covariates adjusted for in the comparative analysis of GLM with TP included sex, age, disease duration, calendar year, extent of UC, and history of lower endoscopies, therapy with steroids, primary sclerosing cholangitis, psoriasis, and CD.

Age was categorized as a binary variable (< 35 years, ≥ 35 years). Disease duration was defined as years since date of first diagnosis of UC in the national patient registers using four categories (< 1, 1–4, 5–9, ≥ 10 years). Extent of disease before or at inclusion was categorized using the Montreal classification [35] and measured as the maximal disease extent ever recorded (E1: ulcerative proctitis, E2: left-sided UC [distal UC], E3: extensive UC [pancolitis], unclassifiable). History of lower endoscopies was defined as the number of colonoscopies and/or sigmoidoscopies performed (no, one, two or more procedures registered) in the 12 months before therapy. History of therapy with steroids was defined as a binary variable (yes, no) as at least two therapies with systemic steroids ≤ 1 year before inclusion. History of primary sclerosing cholangitis, arthropathies, psoriasis, and CD before inclusion was defined as a binary variable (yes, no) using primary and secondary diagnoses. History of therapy with TP was defined as a binary variable (yes, no). History of therapy with biologics was defined as prior use of IFX, ADA, GLM, and vedolizumab as number of different therapies (none, one, two or more). History of therapy with cyclosporine was defined as a binary variable (yes, no) ≤ 1 year before inclusion. The time periods of history of diagnoses and treatments were based on available data. In Denmark, information in the Danish National Patient Register and the Danish National Prescription Register was available since 1977 and 1995, respectively [20, 22]. In Sweden, information was available since 1987 and 2005 [21, 23], respectively.

Age, disease duration, and history of therapies with TP and biologics were included as time-varying variables to account for changes in covariates.

2.5 Statistical Analyses

Descriptive analysis of demographic and clinical characteristics was performed by means of frequency distributions (*N*, %) for categorical variables and as mean and standard deviation for continuous variables.

For each outcome, patients were followed from date of inclusion until date of the first censoring event, defined as the outcome of interest, death, emigration, or end of the study period. The association between exposure to GLM, other anti-TNF agent, and TP and the outcomes was examined using Poisson regression of number of events with the logarithmic transformation of follow-up time as offset [36]. As opposed to using Cox regression, more than one time scale can be handled in a Poisson regression of IRs. In the present study, the following three time scales were included: age, calendar year, and time since inclusion in the study.

The follow-up time was split into single days to handle the time-varying exposure and confounders. Results are presented as IRs and IR ratio (IRR) with corresponding 95% CIs. Associations were evaluated unadjusted and adjusted for potential confounders (i.e., covariates identified by the DAG approach and covariates pre-specified in the protocol).

2.6 Sensitivity Analyses

To examine the robustness of the study findings, we performed nine sensitivity analyses (Table 1). Alternative specifications of the study population, exposure periods, and outcome were evaluated. We also performed a quantitative bias analysis (QBA) [37, 38] for the outcome of all-cause total colectomy to adjust for bias due to under-ascertainment of prior IFX exposure in the Swedish National Patient Register. Specifically, it evaluated the impact on the IRR if prior IFX exposure was completely ascertained. Given that prior IFX exposure may predict a higher risk of all-cause total colectomy for patients treated with either GLM or ADA, missing information on previous IFX use may confound the association between GLM and outcome. Therefore, in the QBA for the outcome of all-cause total colectomy, the comparison was GLM versus

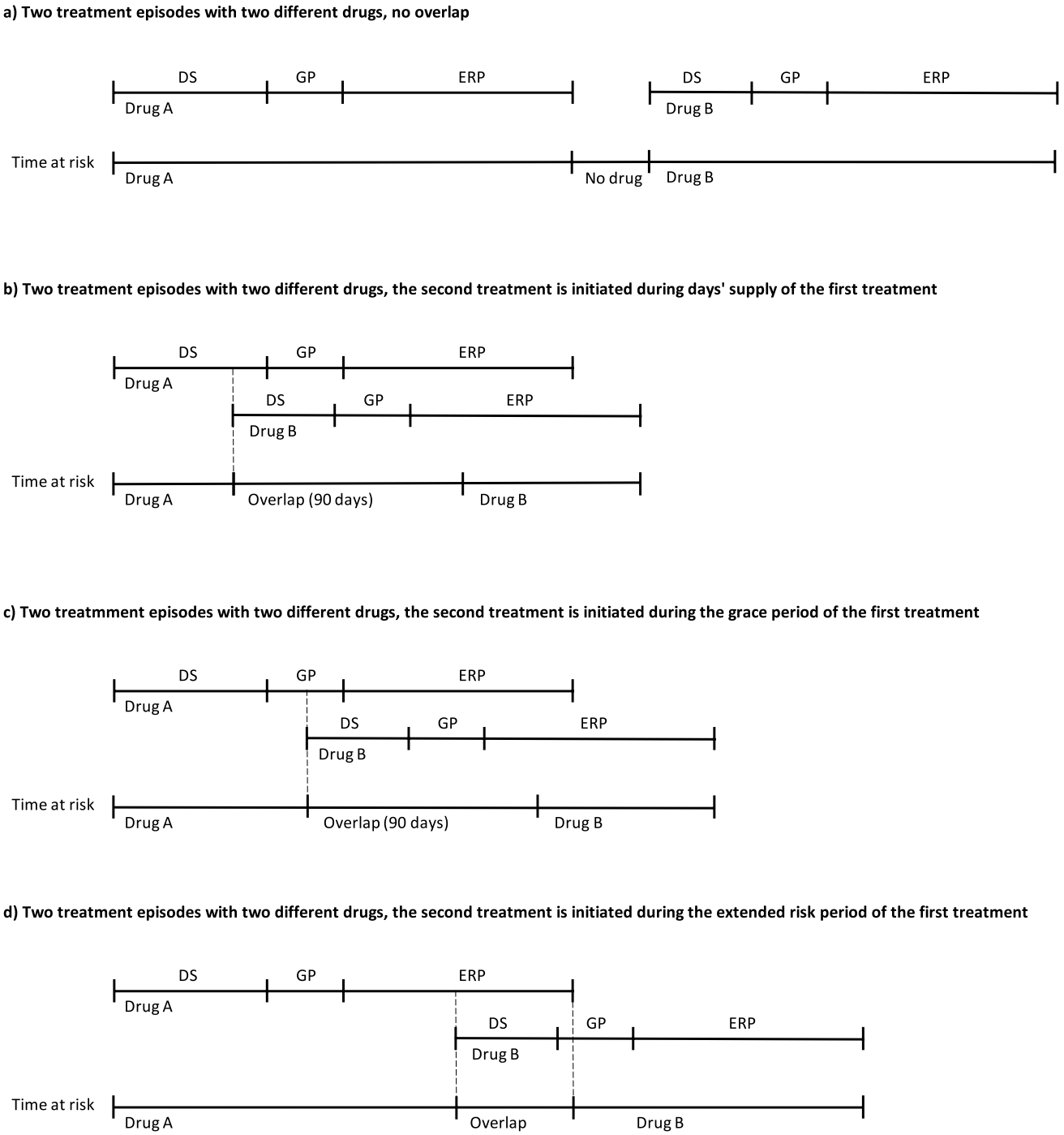


Fig. 2 Illustrations of the construction of treatment episodes and definition of time at risk for all-cause total colectomy for multiple therapies and overlap between therapies with golimumab and other anti-tumor necrosis factor agent. The time at risk is calculated based on days' supply (DS), a 30-day grace period (GP), and a 90-day extended risk period (ERP)

ADA exposures and IFX was adjusted for as an unmeasured confounder.

Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and STATA 17 (StataCorp LLC, TX, USA).

3 Results

Among 156,873 patients with a primary diagnosis of UC before the end of the enrollment period (i.e., 87,177 in Denmark and 69,696 in Sweden), 13,916 patients had a first-time treatment with an anti-TNF agent or TP during the

Table 1 Overview of sensitivity analyses performed

Number	Description
1	Investigating the effect of changing attribution of overlap periods to the previous drug rather than the new drug
2	Investigating the effect of changing the diagnostic criteria of UC from one to two independent registrations of UC as primary discharge diagnosis, combined with having no registered diagnosis of CD
3	Investigating the effect of an increased length of the extended risk window to 6 months
4	Investigating the effect of using CRC as a censoring event
5	Investigating the effect of excluding all patients with a prior history of therapy with biologics other than the biologic study therapies (GLM, IFX or ADA)
6	Investigating the effect of restricting the GLM cohort to patients who were TP naïve at therapy cohort entry in the comparison between GLM and TP because indications for treatment with TP were different in Denmark and Sweden
7	Investigating the effect of exclusion of all-cause total colectomies performed where CRC was registered as the main discharge diagnosis. It was assumed that the remaining all-cause total colectomies were performed due to intractable UC
8	Investigating the effect of accepting any type of colectomy as a relevant outcome
9	Performing a quantitative bias analysis to assess the potential impact of under-ascertainment of IFX exposure in Sweden

ADA adalimumab, *CD* Crohn's disease, *CRC* colorectal cancer, *GLM* golimumab, *IFX* infliximab, *TP* thiopurine, *UC* ulcerative colitis

enrollment period, including 5700 (6.5%) patients in Denmark and 8216 (11.8%) patients in Sweden. Patients with a previous diagnosis of HSTCL, CRC, partial or total colectomy, or treatment with etanercept or certolizumab pegol were excluded. This resulted in a total of 12,646 patients (5177 in Denmark and 7469 in Sweden) included in the analyses (Fig. 3). The proportion of patients with GLM as the initial therapy was 2.8% (3.8% in Denmark and 2.0% in Sweden) compared with 38.0% with other anti-TNF agents (50.8% in Denmark and 29.1% in Sweden) and 59.3% with TP (45.4% in Denmark and 68.9% in Sweden) (Table 2).

3.1 Characteristics of Study Population

Patients in Denmark and Sweden had many similar characteristics at the date of initial inclusion in the study (Table 2). Overall, 47.3% of the patients were aged < 35 years at inclusion, 53.2% were male, and 62.1% had a duration of UC < 5 years at inclusion. Patients exposed to GLM therapy at date of inclusion were older, were more often female, had a longer UC duration, had more severe disease, and had more often been exposed to at least one prior biologic therapy than patients exposed to other therapies at inclusion.

Characteristics of the patients at first treatment with GLM, other anti-TNF agent, and TP during the study period are shown in Table 2 in the ESM. Patients could be included in one, two, or three different treatment categories because of therapy switching. The proportion of patients with at least one GLM therapy was 7.1% (11.5% in Denmark and 4.0% in Sweden). A total of 55.8% had at least one therapy with other anti-TNF agents (71.0% in Denmark and 45.3% in Sweden) (Table 2 in the ESM). Patients exposed to GLM therapy for the first time were older, had a longer UC duration, and had more often been exposed to at least one prior biologic therapy than patients exposed to other therapies for the first time.

3.2 CRC and HSTCL Outcomes

During the study, a total of 68 CRC events (27 in Denmark and 41 in Sweden) and no HSTCL events were reported. Privacy regulations meant that further analysis of the CRC events was not possible because of the low number of events (< 5) in individual exposure categories.

3.3 Association Between GLM and All-Cause Total Colectomy

During the study, 1160 cases of all-cause total colectomy were reported, of which 797 occurred in exposed periods at risk of all-cause total colectomy and were included in the association analysis (Table 3). This included 522 (10.1%) patients with all-cause total colectomy in Denmark and 275 (3.7%) patients in Sweden. The mean follow-up time was 2.4 years and 2.3 years in Denmark and Sweden, respectively.

Given the low number of events of all-cause total colectomy during periods with overlapping therapies with GLM and other anti-TNFs, periods with GLM monotherapy and with GLM overlapping with other anti-TNF were combined.

The IR of all-cause total colectomy per 1000 PYs was substantially higher in Denmark (42.6; 95% CI 38.9–46.2) than in Sweden (16.1; 95% CI 14.2–18.0), especially during periods exposed to GLM and other anti-TNF agents (Fig. 4; Table 3). During periods exposed to GLM (including overlap with other anti-TNF agents), the IRs were 79.0 (95% CI 63.8–97.7) per 1000 PYs in Denmark and 38.5 (95% CI 25.1–59.0) per 1000 PYs in Sweden. Similarly, during periods exposed to other anti-TNF agents (monotherapy), the IRs were 53.6 (95% CI 48.7–59.1) per 1000 PYs in Denmark

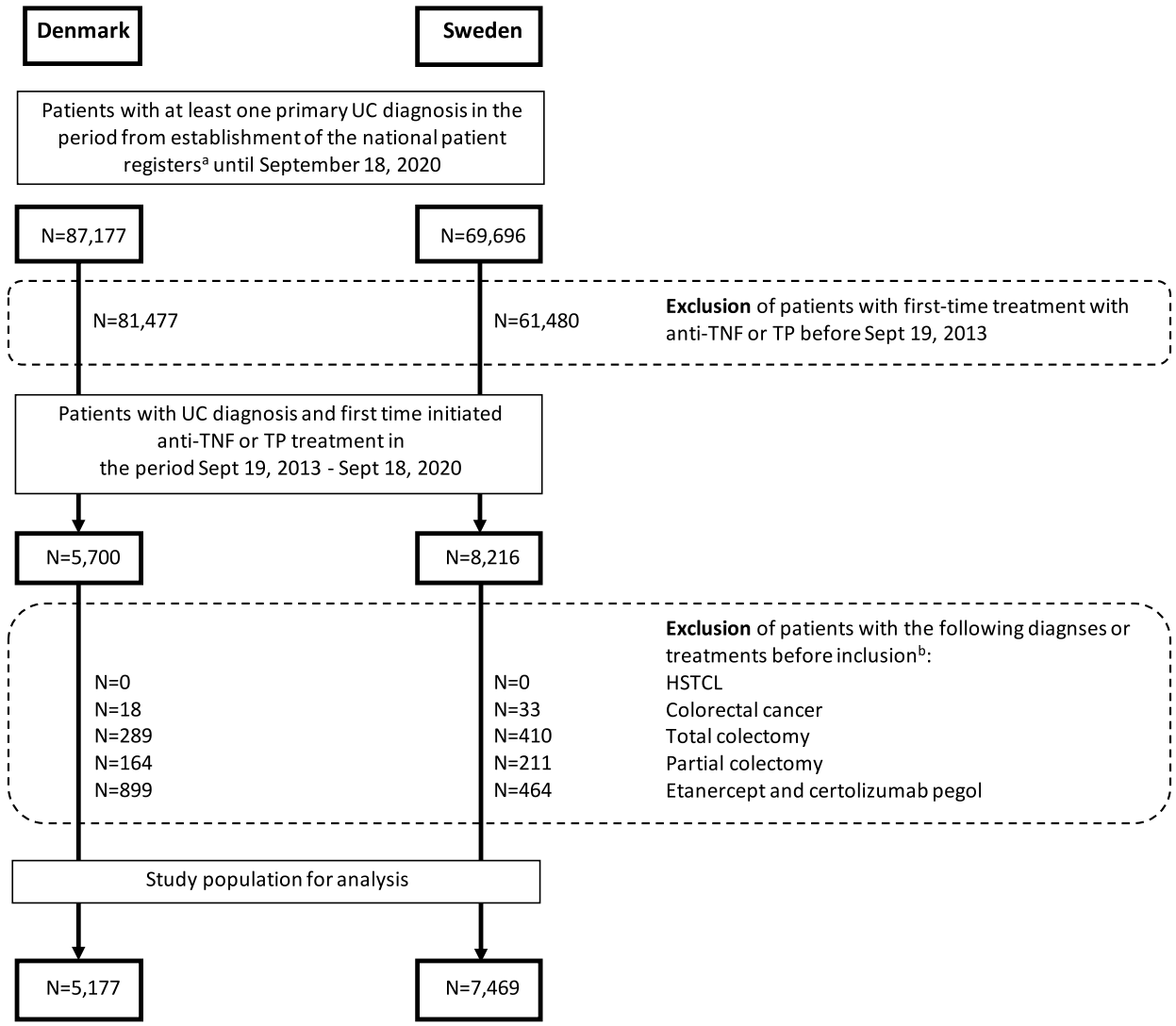


Fig. 3 Data flow diagram of patients with ulcerative colitis (UC) in Denmark and Sweden included in the study population. *HSTCL* hepatosplenic T-cell lymphoma, *TNF* tumor necrosis factor, *TP* thiopurine. [a]The Danish National Patient Register was established in 1977. The Swedish National Patient Register was established in 1987. [b]A patient could have more than one event qualifying for exclusion. The sum of events can therefore exceed the number of patients excluded

and 26.6 (95% CI 22.8–31.0) per 1000 PYs in Sweden. No significant difference was observed in the IR of all-cause total colectomy between exposure to GLM (including overlap with other anti-TNF agents) and other anti-TNF agents (DAG-adjusted IRR 1.28; 95% CI 0.98–1.66 in Denmark and IRR 1.17; 95% CI 0.72–1.90) in Sweden). Further adjustment with pre-specified covariates according to the protocol did not change the magnitude of the measures of association.

In contrast to GLM and other anti-TNF agents, the IR of all-cause total colectomy with TP exposure was similar in Denmark and Sweden (Fig. 4; Table 3). During periods exposed to TP, the IRs were 7.6 (95% CI 5.2–11.1) per 1000 PYs in Denmark and 8.8 (95% CI 7.2–10.8) per 1000 PYs in Sweden. A statistically significant difference was observed in the IR of all-cause total colectomy between exposure to GLM (including overlap with other anti-TNF agents) and TP (DAG-adjusted IRR 13.62; 95% CI 8.73–21.26 in Denmark and IRR 4.52; 95% CI 2.75–7.41 in Sweden). Further adjustment with the pre-specified covariates according to the protocol did not change the magnitude of the measures of association.

3.4 Sensitivity Analyses

Sensitivity analyses supported the overall conclusion of no difference in the IR for all-cause total colectomy between GLM-exposed and other anti-TNF agent-exposed periods

Table 2 Demographic and clinical characteristics of the study population at date of initial inclusion, stratified by treatment at inclusion, $N = 12,646$ patients with ulcerative colitis

Characteristic	*N* (%)	Denmark, $N = 5177$			Sweden, $N = 7469$		
		GLM 199 (3.8)	Other anti-TNF 2630 (50.8)	TP 2348 (45.4)	GLM 151 (2.0)	Other anti-TNF 2172 (29.1)	TP 5146 (68.9)
Mean (SD) age, years	12,646 (100%)	44.6 (14.9)	39.7 (16.8)	41.4 (18.8)	42.9 (14.6)	39.4 (15.9)	38.1 (18.5)
Age group, years)							
< 35	5987 (47.3%)	56 (28.1)	1194 (45.4)	1011 (43.1)	51 (33.8)	980 (45.1)	2695 (52.4)
≥ 35	6659 (52.7%)	143 (71.9)	1436 (54.6)	1337 (56.9)	100 (66.2)	1192 (54.9)	2451 (47.6)
Sex							
Male	6731 (53.2%)	92 (46.2)	1318 (50.1)	1201 (51.1)	63 (41.7)	1153 (53.1)	2904 (56.4)
Female	5915 (46.8%)	107 (53.8)	1312 (49.9)	1147 (48.9)	88 (58.3)	1019 (46.9)	2242 (43.6)
Calendar year of inclusion							
2013	NP	< 5	NP	NP	6 (4.0)	117 (5.4)	238 (4.6)
2014	NP	NP	NP	NP	58 (38.4)	333 (15.3)	780 (15.2)
2015	1781 (14.1%)	22 (11.1)	329 (12.5)	375 (16.0)	28 (18.5)	287 (13.2)	740 (14.4)
2016	NP	21 (10.6)	337 (12.8)	354 (15.1)	NP	NP	784 (15.2)
2017	1757 (13.9%)	27 (13.6)	412 (15.7)	327 (13.9)	20 (13.2)	212 (9.8)	759 (14.7)
2018	1635 (12.9%)	28 (14.1)	336 (12.8)	319 (13.6)	15 (9.9)	260 (12.0)	677 (13.2)
2019	1916 (15.2%)	31 (15.6)	414 (15.7)	281 (12.0)	7 (4.6)	431 (19.8)	752 (14.6)
2020	NP	16 (8.0)	318 (12.1)	188 (8.0)	< 5	NP	416 (8.1)
UC duration (time since first registration of primary UC) in years							
< 1	4551 (36.0%)	11 (5.5)	937 (35.6)	970 (41.3)	5 (3.3)	424 (19.5)	2204 (42.8)
1–4	3305 (26.1%)	33 (16.6)	598 (22.7)	705 (30.0)	39 (25.8)	469 (21.6)	1461 (28.4)
5–9	1883 (14.9%)	57 (28.6)	413 (15.7)	275 (11.7)	36 (23.8)	495 (22.8)	607 (11.8)
≥ 10	2907 (23.0%)	98 (49.2)	682 (25.9)	398 (17.0)	71 (47.0)	784 (36.1)	874 (17.0)
Maximum extent of disease before or same date as inclusion							
E1: ulcerative proctitis	680 (5.4%)	8 (4.0)	127 (4.8)	120 (5.1)	11 (7.3)	119 (5.5)	295 (5.7)
E2: left-sided UC (distal UC)	2105 (16.6%)	13 (6.5)	184 (7.0)	312 (13.3)	18 (11.9)	390 (18.0)	1188 (23.1)
E3: extensive UC (pancolitis)	7783 (61.5%)	163 (81.9)	1903 (72.4)	1502 (64.0)	99 (65.6)	1291 (59.4)	2825 (54.9)
Unclassifiable	2078 (16.4%)	15 (7.5)	416 (15.8)	414 (17.6)	23 (15.2)	372 (17.1)	838 (16.3)
At least two UC primary diagnoses on or before date of inclusion							
No	1953 (15.4%)	24 (12.1)	433 (16.5)	500 (21.3)	12 (7.9)	305 (14.0)	679 (13.2)
Yes	10,693 (84.6%)	175 (87.9)	2197 (83.5)	1848 (78.7)	139 (92.1)	1867 (86.0)	4467 (86.8)
At least two therapies with systemic steroid, ≤ 1 year before date of inclusion							
No	5339 (42.2%)	113 (56.8)	1340 (51.0)	844 (35.9)	80 (53.0)	1081 (49.8)	1881 (36.6)
Yes	7307 (57.8%)	86 (43.2)	1290 (49.0)	1504 (64.1)	71 (47.0)	1091 (50.2)	3265 (63.4)
Prior therapy with cyclosporine, ≤ 1 year before inclusion							
No	NP	199 (100.0)	NP	NP	NP	2165 (99.7)	NP
Yes	NP	0 (0.0)	NP	< 5	NP	7 (0.3)	< 5
Prior diagnosis (primary or secondary diagnosis)[a] before date of inclusion with							
Primary sclerosing cholangitis	NP	< 5	NP	NP	6 (4.0)	78 (3.6)	141 (2.7)
Arthropathies	NP	< 5	NP	< 5	30 (19.9)	222 (10.2)	73 (1.4)
Psoriasis	NP	9 (4.5)	75 (2.9)	15 (0.6)	< 5	36 (1.7)	25 (0.5)
Crohn's disease	2818 (22.3%)	54 (27.1)	643 (24.4)	400 (17.0)	51 (33.8)	766 (35.3)	904 (17.6)
At least one colonoscopy and/or sigmoidoscopy before inclusion							
≤ 1 year	9461 (74.8%)	139 (69.8)	2157 (82.0)	1941 (82.7)	85 (56.3)	1406 (64.7)	3733 (72.5)
≤ 2 years	10,502 (83.1%)	156 (78.4)	2291 (87.1)	2104 (89.6)	105 (69.5)	1644 (75.7)	4203 (81.7)
≤ 3 years	10,958 (86.7%)	171 (85.9)	2366 (90.0)	2160 (92.0)	113 (74.8)	1749 (80.5)	4399 (85.5)
Prior therapy with thiopurine at date of inclusion							
No	2814 (54.6%)	45 (22.6)	1732 (65.9)	NA	51 (33.8)	986 (45.4)	NA
Yes	2338 (45.4%)	154 (77.4)	898 (34.1)	NA	100 (66.2)	1186 (54.6)	NA

Table 2 (continued)

Characteristic	*N* (%)	Denmark, *N* = 5177			Sweden, *N* = 7469		
		GLM 199 (3.8)	Other anti-TNF 2630 (50.8)	TP 2348 (45.4)	GLM 151 (2.0)	Other anti-TNF 2172 (29.1)	TP 5146 (68.9)
Prior therapy with biologic agents (incl IFX, ADA, GLM and vedolizumab) at date of inclusion							
0	NP	49 (24.6)	2352 (89.4)	2348 (100)	93 (61.6)	NP	5146 (100)
1	568 (11.0%)	100 (50.3)	265 (10.1)	NA	50 (33.1)	153 (7.0)	NA
≥ 2	NP	50 (25.1)	13 (0.5)	NA	8 (5.3)	< 5	NA
Vedolizumab	55 (1.1%)	19 (9.5)	27 (1.0)	NA	0 (0.0)	9 (0.4)	NA

Values are expressed as *n* (%) unless stated otherwise

ADA adalimumab, *GLM* golimumab, *IFX* infliximab, *NA* not applicable, *NP* not permissible due to small numbers, *other anti-TNF* infliximab and adalimumab, *SD* standard deviation, *TNF* tumor necrosis factor, *TP* thiopurine, *UC* ulcerative colitis

[a]Patients may enter multiple treatment categories

Table 3 Association between treatment with golimumab and all-cause total colectomy in comparison with other anti-tumor necrosis factor (TNF) agents and thiopurine, in Denmark and Sweden, respectively.

Therapy	*N*	PY	IR per 1000 PY (95% CI)	IRR (95% CI)		
				Unadjusted	Adjusted DAG[a,b]	Adjusted pre-specified[c,d]
Denmark						
GLM[e]	85	1076.5	79.0 (63.8–97.7)	1.47 (1.17–1.86)	1.28 (0.98–1.66)	1.25 (0.96–1.63)
Other anti-TNF	410	7647.2	53.6 (48.7–59.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM	85	1076.5	79.0 (63.8–97.7)	10.36 (6.72–15.97)	13.62 (8.73–21.26)	12.66 (8.08–19.84)
TP	27	3540.9	7.6 (5.2–11.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Sweden						
GLM[e]	21	545.7	38.5 (25.1–59.0)	1.45 (0.92–2.28)	1.17 (0.72–1.90)	1.08 (0.67–1.76)
Other anti-TNF	162	6094.3	26.6 (22.8–31.0)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM	21	545.7	38.5 (25.1–59.0)	4.37 (2.72–7.03)	4.52 (2.75–7.41)	3.85 (2.33–6.36)
TP	92	10,455.1	8.8 (7.2–10.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Values are expressed as numbers (*N*), follow-up time in PYs, IR per 1000 PY, and IRR with corresponding 95% CI for the unadjusted and adjusted analyses

CD Crohn's disease, *CI* confidence interval, *DAG* directed acyclic graph, *GLM* golimumab, *IR* incidence rate, *IRR* incidence rate ratio, *N* number of all-cause total colectomy, *other anti-TNF* infliximab and adalimumab, *PY* person-years, *ref.* reference, *TNF* tumor necrosis factor, *TP* thiopurine, *UC* ulcerative colitis

[a]The following confounders were included in the model according to the DAG approach for the comparison of GLM and other anti-TNF agent: age, disease duration, calendar year, extent of UC, history of sclerosing cholangitis, history of therapy with steroids, and history of therapy with biologics

[b]The following confounders were included in the model according to the DAG approach for the comparison of GLM and TP: age, disease duration, calendar year, extent of UC, history of therapy with steroids, history of sclerosing cholangitis

[c]The following covariates were included in the model according to the protocol for the comparison of GLM and other anti-TNF agent: sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of arthropathies, history of psoriasis, history of CD, history of therapy with TP, and history of therapy with biologics. History of arthropathies was excluded because of a lack of data in the Danish data set

[d]The following covariates were included in the model according to the protocol for the comparison of GLM and TP: sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of psoriasis, and history of CD. History of arthropathies was excluded because of a lack of data in the Danish data set

[e]GLM includes GLM monotherapy and overlap between GLM and other anti-TNF agent

(Table 4). The significantly increased IR of all-cause total colectomy during GLM-exposed periods compared with TP-exposed periods was also observed in the different sensitivity analyses.

The QBA suggested that the IRR for all-cause total colectomy for the comparison of GLM with other anti-TNF-exposed periods in the main analysis could be reduced by

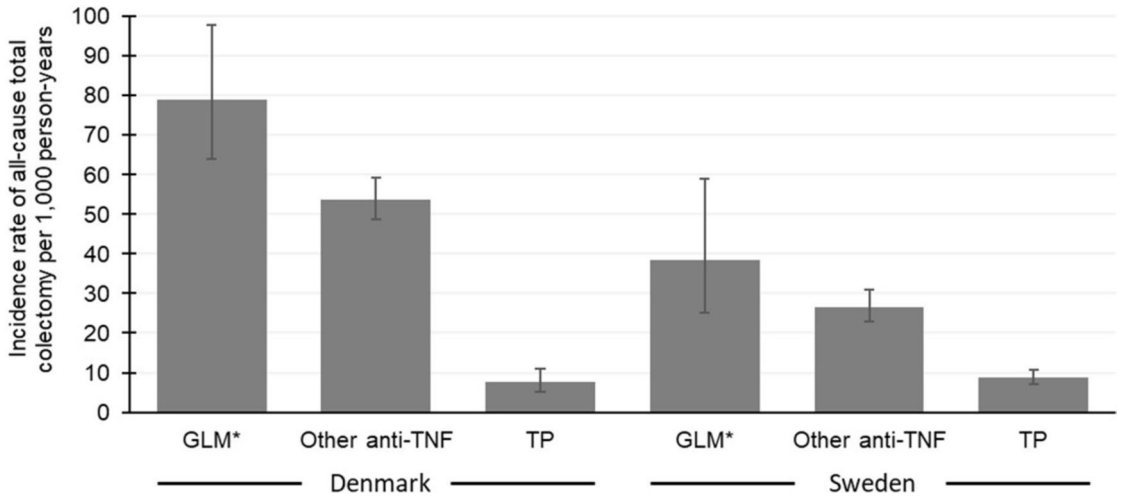


Fig. 4 Incidence rate of all-cause total colectomy during periods exposed to golimumab (GLM), other anti-tumor necrosis factor (TNF) agents, and thiopurine (TP) in Denmark and Sweden. *GLM incidence rates include events and time at risk during GLM monotherapy and overlap between GLM and other anti-TNF agent

about 30% and thereby attenuated toward null if prior IFX exposure was completely ascertained in Sweden (Table 4).

4 Discussion

This observational study used nationwide routinely collected data from national health registers in Denmark and Sweden to provide real-world evidence on the long-term incidence of all-cause total colectomy, CRC, and HSTCL among patients with UC initiating GLM or alternative therapies. To our knowledge, this is the first large-scale, long-term cohort study in UC to evaluate the association between GLM and comparator treatments on all-cause total colectomy, CRC, and HSTCL.

Privacy regulations prevented analysis of a few CRC events. No events of HSTCL were identified.

Overall, the rate of all-cause total colectomy was substantially higher in Denmark than in Sweden. This may at least partly be explained by the finding that the difference was found among patients treated with biologics rather than in patients treated with TP and that the proportion of patients treated with biologics was higher in Denmark than in Sweden. A significantly higher IR of all-cause total colectomy was observed for periods exposed to GLM than for those exposed to TP, particularly in Denmark. However, the IR of all-cause total colectomy during GLM-exposed periods (including overlap with other anti-TNF agents) was not significantly higher than with other anti-TNF agents. Together, these data identify variation in clinical practice patterns between Denmark and Sweden in terms of the use of biologic and TP therapies, and higher rates of colectomy when anti-TNF therapy fails relative to TP therapy, but no significant difference in all-cause colectomy rates between the available anti-TNF therapies.

Several reasons could potentially explain the lower IR of all-cause total colectomy during periods exposed to TP. Patients exposed to TP therapy at date of inclusion had less severe disease and a shorter UC duration than patients with GLM as first therapy at inclusion. Furthermore, it is unlikely that a patient would undergo colectomy following exposure only to TP therapy without being prescribed anti-TNF therapy except for indications other than treatment failure. Indeed, most patients treated with GLM had prior TP therapy. Moreover, longer duration of UC, more severe disease, and a higher proportion of prior biologic use among patients initiating GLM therapy than among those using other anti-TNF agents, suggest that GLM may have been used preferentially after inadequate response to a course of another biologic. For example, 75% of GLM-treated patients in Denmark had been previously treated with another anti-TNF agent, and nearly 10% had been treated with vedolizumab. Importantly, the chance of treatment success is reduced with each successive biologic therapy [39, 40]. Therefore, much of the difference in all-cause colectomy rates between GLM and TP is likely explained by differences in severity of the disease rather than effects of the therapies.

Comparative studies using observational data allow for the assessment of longer term and less frequent outcomes than can be studied in clinical trials. Neither the pivotal registration trials evaluating GLM for the induction and maintenance of remission in patients with moderate to severe UC nor any of the other clinical trials in the development program for GLM had observed an increase in the risk of colectomy. In the study by Weinstein et al. [15], the overall frequency of all-cause colectomy was 4.9% during a 4-year

Table 4 Sensitivity analyses of the association between treatment with golimumab (GLM) and all-cause total colectomy in comparison with other anti-tumor necrosis factor (TNF) agent and thiopurine (TP), in Denmark and Sweden, respectively

Therapy	*N*	PY	IR per 1000 PY (95% CI)	IRR (95% CI)		
				Unadjusted	Adjusted DAG[a,b]	Adjusted pre-specified[c,d]
1. Attributing overlap periods to the previous drug rather than the new drug						
Denmark						
GLM[e]	66	986.4	66.9 (52.6–85.2)	1.21 (0.93–1.56)	1.05 (0.79–1.40)	1.05 (0.79–1.39)
Other anti-TNF	429	7736.3	55.5 (50.4–61.0)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Sweden						
GLM[e]	18	527.8	34.1 (21.5–54.1)	1.26 (0.78–2.06)	1.04 (0.62–1.73)	0.97 (0.58–1.62)
Other anti-TNF	165	6112.3	27.0 (23.2–31.4)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
2. Changing the UC criteria to at least two UC diagnoses and no CD diagnosis						
Denmark						
GLM[e]	68	847.5	80.2 (63.3–101.8)	1.23 (0.95–1.60)	1.14 (0.84–1.54)	1.19 (0.88–1.60)
Other anti-TNF	321	4932.0	65.1 (58.3–72.6)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM	68	847.5	80.2 (63.3–101.8)	9.96 (6.10–16.24)	13.48 (8.18–22.22)	12.69 (7.66–21.00)
TP	21	2605.9	8.1 (5.3–12.4)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Sweden						
GLM[e]	13	356.6	36.5 (21.2–62.8)	1.20 (0.67–2.13)	1.03 (0.57–1.89)	0.99 (0.54–1.81)
Other anti-TNF	103	3384.5	30.4 (25.1–36.9)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM[e]	13	356.6	36.5 (21.2–62.8)	4.44 (2.4,4 8.06)	4.94 (266–9.17)	4.50 (2.42–8.39)
TP	64	7790.2	8.2 (6.4–10.5)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
3. Increasing extended risk window to 6 months						
Denmark						
GLM[e]	94	1196.0	78.6 (64.2–96.2)	1.49 (1.19–1.86)	1.25 (0.97–1.60)	1.25 (0.97–1.60)
Other anti-TNF	432	8167.0	52.9 (48.1–58.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM	94	1196.0	78.6 (64.2–96.2)	9.98 (6.65–14.98)	13.00 (8.57–19.75)	12.15 (7.97–18.51)
TP	31	3937.5	7.9 (5.5–11.2)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Sweden						
GLM[e]	22	596.4	36.9 (24.3–56.0)	1.28 (0.83–2.00)	1.07 (0.67–1.72)	0.98 (0.61–1.57)
Other anti-TNF	188	6552.6	28.7 (24.9–33.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM	22	596.4	36.9 (24.3–56.0)	3.76 (2.38–5.95)	3.79 (2.35 6.11)	3.24 (2.00–5.26)
TP	110	11,226.2	9.8 (8.1–11.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
4. CRC as a censoring event						
Denmark						
GLM[e]	85	1076.5	79.0 (63.8–97.7)	1.48 (1.17–1.87)	1.28 (0.98–1.66)	1.26 (0.97–1.64)
Other anti-TNF	407	7642.1	53.3 (48.3–58.7)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM	85	1076.5	79.0 (63.8–97.7)	10.75 (6.93–16.68)	14.27 (9.09–22.41)	13.20 (8.38–20.82)
TP	26	3539.6	7.3 (5.0–10.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Sweden						
GLM[e]	21	545.5	38.5 (25.1–59.0)	1.49 (0.95–2.36)	1.19 (0.73–1.93)	1.10 (0.67–1.79)
Other anti-TNF	157	6093.9	25.8 (22.0–30.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM[f]	21	545.5	38.5 (25.1–59.0)	4.68 (2.90–7.54)	5.02 (3.04–8.27)	4.31 (2.60–7.15)
TP	86	10,450.3	8.2 (6.7–10.2)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
5. Excluding all patients with a history of biologic therapies other than the biologic study therapies (GLM, IFX, or ADA)						
Denmark						
GLM[e]	43	620.9	69.3 (51.4–93.4)	1.20 (0.87–1.65)	1.36 (0.95–1.96)	1.26 (0.88–1.81)
Other anti-TNF	322	5590.2	57.6 (51.6–64.2)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM	43	620.9	69.3 (51.4–93.4)	8.29 (5.13–13.42)	11.99 (7.22–19.90)	11.56 (6.93–19.29)
TP	27	3233.0	8.4 (5.7–12.2)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Sweden						
GLM[e]	20	505.6	39.6 (25.5–61.3)	1.50 (0.94–2.39)	1.24 (0.75–2.05)	1.15 (0.70–1.90)
Other anti-TNF	151	5729.4	26.4 (22.5–30.9)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM	20	505.6	39.6 (25.5–61.3)	4.45 (2.74–7.22)	4.74 (2.86–7.88)	3.99 (2.38–6.67)
TP	92	10,352.9	8.9 (7.2–10.9)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Table 4 (continued)

Therapy	*N*	PY	IR per 1000 PY (95% CI)	IRR (95% CI)		
				Unadjusted	Adjusted DAG[a,b]	Adjusted pre-specified[c,d]
6. Restricting the GLM cohort to patients who were TP naïve at therapy cohort entry in the comparison between GLM and TP						
Denmark						
GLM[e]	17	269.0	63.2 (39.3–101.7)	8.29 (4.52–15.21)	12.10 (6.30, 23.24)	9.95 (5.04, 19.63)
TP	27	3540.9	7.6 (5.2–11.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Sweden						
GLM[e]	0	144.2	0.0 (0.0–0.0)	No analyses were performed due to low numbers		
TP	92	10,455.1	8.8 (7.2–10.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
7. Excluding all-cause total colectomies where underlying primary diagnosis is CRC						
Denmark						
GLM[e]	84	1076.5	78.0 (63.0–96.6)	1.47 (1.16–1.85)	1.26 (0.97–1.65)	1.24 (0.96–1.62)
Other anti-TNF	407	7646.2	53.2 (48.3–58.7)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM	84	1076.5	78.0 (63.0–96.6)	10.63 (6.85–16.50)	14.19 (9.03–22.30)	13.08 (8.29–20.63)
TP	26	3540.9	7.3 (5.0–10.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Sweden						
GLM[e]	21	545.7	38.5 (25.1–59.0)	1.48 (0.94–2.34)	1.19 (0.73–1.93)	1.10 (0.67–1.78)
Other anti-TNF	158	6094.3	25.9 (22.2–30.3)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM	21	545.7	38.5 (25.1–59.0)	4.62 (2.87–7.45)	4.97 (3.01–8.18)	4.29 (2.59–7.11)
TP	87	10,455.1	8.3 (6.7–10.3)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
8. Including any type (e.g. partial or total) of colectomy as the outcome						
Denmark						
GLM[e]	87	1074.7	81.0 (65.6–99.9)	1.41 (1.12–1.77)	1.21 (0.94–1.57)	1.22 (0.94–1.57)
Other anti-TNF	437	7597.2	57.5 (52.4–63.2)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM	87	1074.7	81.0 (65.6–99.9)	8.41 (5.66–12.51)	11.57 (7.67–17.45)	10.74 (7.09–16.27)
TP	34	3533.8	9.6 (6.9–13.5)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Sweden						
GLM[e]	24	542.5	44.2 (29.7–66.0)	1.47 (0.96–2.25)	1.25 (0.80–1.97)	1.17 (0.74–1.85)
Other anti-TNF	183	6071.6	30.1 (26.1–34.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
GLM	24	542.5	44.2 (29.7–66.0)	4.52 (2.90–7.06)	4.79 (3.01–7.63)	4.08 (2.55–6.53)
TP	102	10,431.2	9.8 (8.1–11.9)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
9. QBA, Sweden. Adjusting for unmeasured confounder of prior IFX exposure (GLM vs ADA)						
Main analysis						
GLM[f]	21	548.9	38.3 (24.9–58.7)	1.56 (0.98–2.47)	1.50 (0.94–2.39)	1.39 (0.87–2.21)
ADA	129	5260.7	24.5 (20.6–29.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
QBA						
GLM[f]	21	548.9	38.3 (24.9–58.7)	1.14 (0.92–1.43)	1.09 (0.87–1.38)	1.05 (0.83–1.31)
ADA	129	5260.7	24.5 (20.6–29.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Values are expressed as numbers (*N*), follow-up time in PY, IR per 1,000 PY, and IRR with corresponding 95% CI for the unadjusted and adjusted analyses

ADA adalimumab, *CD* Crohn's disease, *CI* confidence interval, *DAG* directed acyclic graph, *GLM* golimumab, *IR* incidence rate, *IRR* incidence rate ratio, *N* number of all-cause total colectomy, *other anti-TNF* infliximab and adalimumab, *PY* person-years, *QBA* quantitative bias analysis, *ref.* reference, *TNF* tumor necrosis factor, *TP* thiopurine, *UC* ulcerative colitis

[a]The following confounders were included in the model according to the DAG approach for the comparison of GLM and other anti-TNF: age, disease duration, calendar year, extent of UC, history of primary sclerosing cholangitis, history of therapy with steroids, and history of therapy with biologics

[b]The following confounders were included in the model according to the DAG approach for the comparison of GLM and TP: age, disease duration, calendar year, extent of UC, history of therapy with steroids, history of primary sclerosing cholangitis

[c]The following covariates were included in the model according to the protocol for the comparison of GLM and other anti-TNF: sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of primary sclerosing cholangitis, history of arthropathies, history of psoriasis, history of CD, history of therapy with TP, and history of therapy with biologics. History of arthropathies was excluded because of a lack of data in the Danish data set

[d]The following covariates were included in the model according to the protocol for the comparison of GLM and TP: sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of primary sclerosing cholangitis, history of psoriasis, and history of CD. History of arthropathies was excluded because of a lack of data in the Danish data set

[e]GLM includes GLM monotherapy and overlap between GLM and other anti-TNF

[f]GLM includes GLM monotherapy and overlap between GLM and ADA

study period, including 4.2% of participants undergoing colectomy within the first year of the maintenance study with an additional 1.4% of participants undergoing colectomy during the 3-year extension study. In the present study with up to 8 years follow-up, 10.1% had an all-cause total colectomy in Denmark and 3.7% in Sweden.

In a retrospective chart review study across 16 sites in the UK, Hoque et al. [16] compared the risk of colectomy in 183 patients with UC who initiated treatment with GLM or ADA (87 and 96 patients, respectively). Demographic and clinical characteristics were generally similar between the two treatment groups. Approximately 80% of the patients received GLM or ADA as a first-line biologic. After 1 year of treatment, 8.2% underwent colectomy. No significant difference in colectomy-free survival was observed between patients initiating treatment with GLM and ADA. These findings are consistent with those in our study, although ours included up to 8 years of follow-up and a much larger sample size.

In a retrospective cohort study including 1268 patients from the Korean National Health Insurance database as new anti-TNF users with IFX, ADA, or GLM (713, 433, and 122 patients), 0.9% (12 patients) underwent colectomy within 1 year. No significant difference in risk of colectomy was found [17]. The findings in this study also support the results of the present study. However, the Korean study had a shorter follow-up period, a smaller sample size, and a lower proportion of colectomies.

4.1 Strengths and Limitations

Our study has several strengths, including the use of real-world evidence from a large sample size with many years of follow-up. Nationwide data collected independently from the study and during routine clinical encounters from patients with UC in Denmark and Sweden are generally considered to be of high quality in terms of completeness and validity [25]. Inclusion of data from two different countries increases generalizability. However, the generalizability may be affected by differences between countries in clinical guidelines, treatment strategies (e.g., colectomy rate and TP indications), and the registration of the surgical procedure codes [41]. Using register-based nationwide populations limits selection bias. Additionally, to limit the risk of unnecessary adjustment and overadjustment bias, the minimal sufficient adjustment set of confounders to include in the association analyses was identified using the DAG approach.

The study also has several limitations. Periods with overlap between GLM and other anti-TNF agents were allocated to GLM therapy, which could result in bias against GLM because the overlap periods could reflect a period of more severe disease and thus a higher risk of colectomy. The sensitivity analysis allocating the overlap period to the previous therapy instead of entirely to GLM eliminated the slightly higher risk of colectomy in Denmark and further supports a bias against GLM when allocating the overlapping period to GLM therapy in the primary analysis. In addition, all-cause total colectomy was used as a proxy for loss of efficacy of medical treatment. Other less frequent indications for colectomy, such as patient preferences and adverse events from medical treatment, may cause misclassification. The study also lacked a direct measure of disease activity and relied on a few proxy variables (e.g., UC duration, extent of disease, number of colonoscopies/sigmoidoscopies, and prior therapies). Therefore, the association analyses may not have been optimally adjusted with respect to disease activity, and confounding by indication may have occurred. Moreover, clinical practice during the observation period may have changed. Several studies from both Denmark and Sweden have shown a steady increase in the use of biologics during recent decades, which might indicate a more liberal use of these therapies and in milder cases [42]. The present study cannot account for changes in clinical guidelines and practice. However, the analyses were adjusted for calendar year, which may account for these changes to some extent.

Another limitation is the lack of inclusion of recently approved therapies for moderate to severe UC. Since the initial protocol approval, several therapies have been approved for this indication, including vedolizumab (2014), tofacitinib (2018), ustekinumab (2019), ozanimod (2020), upadacitinib (2022), and etrasimod (2024). Vedolizumab was included as a covariate. However, this study does not inform the relative safety of these newer therapies.

Some of the patients diagnosed with UC might have had CD, which may cause a potential bias of patients included. Because GLM is not approved for CD, and total colectomy is less common among patients with CD, there is a greater potential for CD versus UC misclassification in patients treated with the comparator therapies. A sensitivity analysis restricted to patients with two independent registrations of UC and no registered CD diagnosis did not change the overall conclusion.

The study did not evaluate the effect of dosing or early dose optimization of the treatments on risk of all-cause total colectomy, although studies have shown a beneficial effect of dose escalation [39].

Therapy discontinuation was not registered and had to be inferred by the absence of additional registrations of the therapy. For this reason, it is difficult to distinguish between switch of therapies versus discontinuation and later re-uptake of therapy after a period without therapy, making it difficult to evaluate the effect of individual specific therapies. Although this is considered a limitation, sensitivity analyses using alternative risk window definitions in various scenarios confirmed the principal findings.

Information about IFX use in Sweden was extracted from the Swedish National Patient Register, but the capture of therapies administered in the hospital setting was expected

to be incomplete. A QBA was performed as a sensitivity analysis to investigate the impact of under-registration of IFX infusion therapy in the Swedish National Patient Register. A reduction of about 30% was observed in the risk of all-cause total colectomy after adjusting for prior IFX exposure, indicating some degree of bias against GLM due to under-ascertainment of prior IFX exposure in Sweden.

Despite the large number of patients with UC in Denmark and Sweden, the inclusion criteria resulted in a limited sample size and reduced power. Furthermore, periods exposed to GLM monotherapy could not be examined because of the small numbers in the overlap category, which necessitated combining the overlap category with GLM monotherapy to avoid further masking of results. Furthermore, few CRC events and the absence of any HSTCL events prevented the examination and reporting of CRC and HSTCL as an outcome.

5 Conclusions

This observational cohort study of patients with moderate to severe UC performed in Denmark and Sweden using nationwide health registers evaluated the incidence of prespecified outcomes in patients exposed to GLM compared with patients exposed to other anti-TNF therapies and TP. The study did not observe a significant difference in IRs of all-cause total colectomy between GLM and other anti-TNF therapies. Although the incidence of all-cause total colectomy was several times higher in patients with GLM exposure than in those with TP exposure, especially in Denmark, this finding may be due to confounding by indication. There were no events of HSTCL and too few events of CRC to be presented because of privacy regulations.

Collectively, this real-world study provided no evidence that GLM poses an increased incidence of all-cause total colectomy compared with other anti-TNF agents for the treatment of UC.

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Declarations

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Conflict of interest JL has consulted or served on an advisory board for AbbVie, Amgen, Arena Pharmaceuticals, Bridge Biotherapeutics, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, Entasis Therapeutics, Galapagos, Gilead, Janssen Pharmaceuticals, Samsung Bioepis, Merck, Nestle Health Science, UCB, Pfizer, Protagonist Therapeutics, Sanofi, and Scipher Medicine; has received research funding from Nestle Health Science, Takeda, Janssen Pharmaceuticals, and AbbVie; has received educational grants from Takeda and Janssen; and has received in-kind support from Eli Lilly and Company. VA is member of the Merck advisory board and has consulted for Janssen. LM, SMH, and LK were employees at ApHER/MedEngine while the study was conducted. ZH, DDH, and CW are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may hold stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. SE and AK were employees at Janssen while the study was conducted. KB and AG were responsible for the study in Sweden as consultants for ApHER/MedEngine. AKE, LCT, TMK, MSK, SK, FRH, NQ, and EH have no conflicts of interest to declare.

Availability of data and material Register-based micro-level data sharing is not permitted. The researchers (AKE and AG) have access to data at secure servers at the Danish Health Data Authority and at secure local servers.

Ethics approval Different ethical approvals are needed in Denmark and Sweden [26, 43]. In Denmark, register-based studies do not need ethical approval [25]. The study was approved by the Research and Innovation Organisation at University of Southern Denmark (reference number: 10.186). The Swedish Ethical Review Authority approved the initial study protocol (reference 2019-04411) and amendments (reference 2020-00038). In Denmark, a minimum of five observations is needed to present results because of privacy regulations. Consequently, numbers less than five are masked as "<5" for results. So that the masked number cannot be calculated, further results have been masked and indicated as not permissible.

Consent to participate Not applicable.

Consent to publication Not applicable.

Code availability Not applicable.

Author contributions AKE: conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing – original draft, writing – review and editing, visualization, and project administration. LCT: conceptualization, methodology, software, investigation, resources, data curation, writing – review and editing, and supervision. TMK: conceptualization, methodology, software, investigation, resources, data curation, and writing – review and editing. MSK: conceptualization, methodology, software, investigation, resources, data curation, and writing – review and editing. SK: methodology, software, resources, writing – review and editing, and visualization. FRH: methodology, software, resources, and writing – review and editing. NQ: conceptualization, investigation, writing – review and editing, visualization, and supervision. VA: conceptualization, investigation, writing – review and editing, visualization, and supervision. EH: conceptualization, investigation, writing – review and editing, visualization, and supervision. JL: conceptualization, investigation, writing – review and editing, and visualization. LM: software, formal analysis, investigation, resources, data curation, writing – review and editing, and project administration. SMH: conceptualization, investigation, writing – review and editing, and project administration. LK

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References

1. Lophaven SN, Lynge E, Burisch J. The incidence of inflammatory bowel disease in Denmark 1980–2013: a nationwide cohort study. Aliment Pharmacol Ther. 2017;45(7):961–72.
2. Agrawal M, Christensen HS, Bøgsted M, Colombel JF, Jess T, Allin KH. The rising burden of inflammatory bowel disease in Denmark over two decades: a Nationwide Cohort Study. Gastroenterology. 2022;163(6):1547-1554.e5.
3. Eriksson C, Cao Y, Rundquist S, Zhulina Y, Henriksson I, Montgomery S, Halfvarson J. Changes in medical management and colectomy rates: a population-based cohort study on the epidemiology and natural history of ulcerative colitis in Örebro, Sweden, 1963–2010. Aliment Pharmacol Ther. 2017;46(8):748–57.
4. Singh S, Loftus EV Jr, Limketkai BN, Haydek JP, Agrawal M, Scott FI, Ananthakrishnan AN, AGA Clinical Guidelines Committee. AGA living clinical practice guideline on pharmacological management of moderate-to-severe ulcerative colitis. Gastroenterology. 2024;167(7):1307–43.
5. Reich KM, Chang HJ, Rezaie A, Wang H, Goodman KJ, Kaplan GG, Svenson LW, Lees G, Fedorak RN, Kroeker KI. The incidence rate of colectomy for medically refractory ulcerative colitis has declined in parallel with increasing anti-TNF use: a time-trend study. Aliment Pharmacol Ther. 2014;40(6):629–38.
6. Park SC, Jeen YT. Current and emerging biologics for ulcerative colitis. Gut Liver. 2015;9(1):18–27.
7. Meier J, Sturm A. Current treatment of ulcerative colitis. World J Gastroenterol. 2011;17(27):3204–12.
8. Monstad IL, Solberg IC, Cvancarova M, Hovde O, Henriksen M, Huppertz-Hauss G, Gunther E, Moum BA, Stray N, Vatn M, Hoie O, Jahnsen J. Outcome of ulcerative colitis 20 years after diagnosis in a prospective population-based inception cohort from south-eastern Norway, the IBSEN study. J Crohns Colitis. 2021;15(6):969–79.
9. Filippi J, Allen PB, Hebuterne X, Peyrin-Biroulet L. Does anti-TNF therapy reduce the requirement for surgery in ulcerative colitis? A systematic review. Curr Drug Targets. 2011;12(10):1440–7.
10. Cañas-Ventura A, Márquez L, Ricart E, Domènech E, Gisbert JP, García-Sanchez V, Marín-Jiménez I, Rodriguez-Moranta F, Gomollón F, Calvet X, Merino O, Garcia-Planella E, Vázquez-Romero N, Esteve M, Iborra M, Gutiérrez A, Vera M, Andreu M, on behalf of Spanish GETECCU group (ENEIDA project). Risk of colectomy in patients with ulcerative colitis under thiopurine treatment. J Crohns Colitis. 2014;8(10):1287–93.
11. Solberg IC, Lygren I, Jahnsen J, Aadland E, Høie O, Cvancarova M, Bernklev T, Henriksen M, Sauar J, Vatn MH, Moum B, IBSEN Study Group. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scand J Gastroenterol. 2009;44(4):431–40.
12. Zhou Q, Shen ZF, Wu BS, Xu CB, He ZQ, Chen T, Shang HT, Xie CF, Huang SY, Chen YG, Chen HB, Han ST. Risk of colorectal cancer in ulcerative colitis patients: a systematic review and meta-analysis. Gastroenterol Res Pract. 2019:5363261.
13. Olén O, Erichsen R, Sachs MC, Pedersen L, Halfvarson J, Askling J, Ekbom A, Sørensen HT, Ludvigsson JF. Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. Lancet. 2020;395(10218):123–31.
14. Herrinton LJ, Liu L, Abramson O, Jaffe ES. The incidence of hepatosplenic T-cell lymphoma in a large managed care organization, with reference to anti-tumor necrosis factor therapy, Northern California, 2000–2006. Pharmacoepidemiol Drug Saf. 2012;21(1):49–52.
15. Weinstein CLJ, Meehan AG, Govoni M, Lin J, Reinisch W. Low occurrence of colectomy with long-term (up to 4 years) golimumab treatment in patients with moderate-to-severe active ulcerative colitis: data from the PURSUIT maintenance and long-term extension studies. Crohn's & Colitis 360. 2023;5(3):1–8.
16. Hoque S, Puenpatom A, Boccaletti S, Green C, Black CM, Roberts J, Rajkovic I, Milligan G. Treatment persistence and colectomy-free outcomes in patients with ulcerative colitis receiving golimumab or adalimumab: a UK experience. BMJ Open Gastroenterol. 2020;7(1): e000476.
17. Shin JY, Park HM, Lee MY, Jeon JY, Yoo HJ, Ye BD. Real-world incidence of suboptimal response to anti-tumor necrosis factor therapy for ulcerative colitis: a nationwide population-based study. Gut Liver. 2021;15(6):867–77.
18. Pedersen CB. The Danish Civil Registration System. Scand J Pub Health. 2011;39(7 Suppl):22–5.
19. Ludvigsson JF, Almqvist C, Bonamy AKE, Ljung R, Michaelsson K, Neovius M, Stephansson O, Weiman Y. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125–36.
20. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Pub Health. 2011;39(7 Suppl):30–3.
21. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
22. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health. 2011;39(7 Suppl):38–41.
23. Wettermark B, Zoëga H, Furu K, Korhonen M, Hallas J, Nørgaard M, Almarsdottir A, Andersen M, Andersson Sundell K, Bergman U, Helin-Salmivaara A, Hoffmann M, Kieler H, Martikainen J, Mortensen M, Petzold M, Wallach-Kildemoes H, Wallin C, Sørensen H. The Nordic prescription databases as a resource for pharmacoepidemiological research: a literature review. Pharmacoepidemiol Drug Saf. 2013;22(7):691–9.

24. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24:659–67.
25. Thygesen LC, Daasnes C, Thaulow I, Bronnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health. 2011;39(7 Suppl):12–6.
26. Laugesen K, Ludvigsson JF, Schmidt M, Gissler M, Valdimarsdottir UA, Lunde A, Sørensen HT. Nordic health registry-based research: a review of health care systems and key registries. Clin Epidemiol. 2021;13:533–54.
27. Albæk Jacobsen H, Jess T, Larsen L. Validity of inflammatory bowel disease diagnoses in the Danish National Patient Registry: a population-based study from the North Denmark Region. Clin Epidemiol. 2022;14:1099–109.
28. Jacobsson GL, Sternegård E, Olén O, Myrelid P, Ljung R, Strid H, Halfvarson J, Ludvigsson JF. Validating inflammatory bowel disease (IBD) in the Swedish National Patient Register and the Swedish Quality Register for IBD (SWIBREG). Scand J Gastroenterol. 2017;52(2):216–21.
29. Erichsen R, Sværke C, Tøttrup A. The coding quality of acute total colectomy in inflammatory bowel disease patients in a nationwide hospital registry. Pharmacoepidemiol Drug Saf. 2011;20(S1):S165–6.
30. Final study report for MK-8259-012. Available at: https://catalogues.ema.europa.eu/system/files/2024-06/MK-8259-013-CSR-Final-Report-may-2024-final-redaction_1.pdf.
31. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10:37–48.
32. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology. 2011;22(5):745.
33. Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package "dagitty." Int J Epidemiol. 2016;45(6):1887–94.
34. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol. 2008;8:70.
35. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55:749–53.
36. Laird N, Olivier D. Covariance analysis of censored survival data using log-linear analysis techniques. J Am Stat Assoc. 1981;76(374):231–40.
37. Lash TL, Schmidt M, Jensen AØ, Engebjerg MC. Methods to apply probabilistic bias analysis to summary estimates of association. Pharmacoepidemiol Drug Saf. 2010;19(6):638–44.
38. Lash TL, Fox MP, Fink AK. Applying quantitative bias analysis to epidemiologic data. Berlin: Springer; 2009. p. 126–8.
39. Taxonera C, Rodriguez C, Bertoletti F, Menchén L, Arribas J, Sierra M, Arias L, Martínez-Montiel P, Juan A, Iglesias E, Algaba A, Manceñido N, Rivero M, Barreiro-de Acosta M, López-Serrano P, Argüelles-Arias F, Gutiérrez A, Busquets D, Gisbert JP, Olivares D, Calvo M, Alba C. Clinical outcomes of golimumab as first, second or third anti-TNF agent in patients with moderate-to-severe ulcerative colitis. Inflamm Bowel Dis. 2017;23(8):1394–402.
40. Iborra M, Pérez-Gisbert J, Bosca-Watts MM, López-García A, García-Sánchez V, López-Sanromán A, Hinojosa E, Márquez L, García-López S, Chaparro M, Aceituno M, Calafat M, Guardiola J, Belloc B, Ber Y, Bujanda L, Beltrán B, Rodríguez-Gutiérrez C, Barrio J, Cabriada JL, Rivero M, Camargo R, van Domselaar M, Villoria A, Schuterman HS, Hervás D, Nos P, Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU). Effectiveness of adalimumab for the treatment of ulcerative colitis in clinical practice: comparison between anti-tumour necrosis factor-naïve and non-naïve patients. J Gastroenterol. 2017;52(7):788–99.
41. Maret-Ouda J, Tao W, Wahlin K, Lagergren J. Nordic registry-based cohort studies: possibilities and pitfalls when combining Nordic registry data. Scand J Public Health. 2017;45(17_suppl):14–9.
42. Zhao M, Sall Jensen M, Knudsen T, Kelsen J, Coskun M, Kjellberg J, Burisch J. Trends in the use of biologicals and their treatment outcomes among patients with inflammatory bowel diseases: a Danish nationwide cohort study. Aliment Pharmacol Ther. 2022;55(5):541–57.
43. Ludvigsson JF, Haberg SE, Knudsen GP, Lafolie P, Zoega H, Sarkkola C, von Kraemer S, Weiderpass E, Nørgaard M. Ethical aspects of registry-based research in the Nordic countries. Clin Epidemiol. 2015;7:491–508.

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