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Off-label prescriptions of drugs used for the treatment of Crohn's disease or ulcerative colitis

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Abstract

Background: Off-label prescribing is encountered across various fields of medicine and creates alternative treatment options, but is associated with unknown safety risks. The use of off-label drugs for the treatment of patients with inflammatory bowel diseases (IBD) has not been characterised before.

Aim: To assess the proportion and characteristics of off-label prescribing for IBD in tertiary care centres in the Netherlands.

Methods: A prospective database of IBD patients from all Dutch university hospitals was used to collect data on drug prescriptions for IBD and demographics. Drugs were classified as off-label if they were unlicensed for Crohn's disease and/or ulcerative colitis by the Medicines Evaluation Board. Uni- and multivariable analyses were used to identify patient-specific characteristics predictive of increased off-label use.

Results: For the induction and/or maintenance treatment of 4583 IBD patients, 12 651 historical and current drug records were available in the database. Of these, 2374 (19%) were considered off-label prescriptions. Out of 4583 IBD patients, 1477 (32%) were exposed to off-label drugs. Commonly prescribed off-label IBD drugs were mercaptopurine (18%), beclomethasone (12%), thioguanine (4%) and allopurinol (3%). Non-thiopurine/methotrexate off-label drugs were prescribed in 243 patients (6%), including biological agents or tofacitinib in 47 IBD patients (1%). Off-label prescriptions were more common in ulcerative colitis than Crohn's disease (37% vs 29%, $P < 0.001$). Smokers and patients that received ≥5 drug types during their disease course were more likely to be exposed to off-label drugs (smoking 33% vs 27% and multiple drug use 66% vs 22%, both $P < 0.001$).

Conclusion: About one-fifth of prescriptions for IBD were off-label and one-third of IBD patients, especially ulcerative colitis patients, were exposed to off-label drugs.

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1 | INTRODUCTION

Off-label drug prescribing is widespread in daily clinical practice and includes the use of drugs outside the licensed indication, dosage, route of administration or age.[1] Examples of widely prescribed off-label drugs include the use of beta-blockers for anxiety, tricyclic antidepressants for chronic pain and oral contraception to treat endometriosis or acne.

Off-label drugs may create alternative therapeutic options, but have also been associated with safety risks since they are under-evaluated for unlicensed indications.[2] A lack of drug approval by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) generally means a shortage of scientific scrutiny as compared to labelled indications.[3] In a large Canadian cohort, the rate of preventable adverse drug reactions was considerably higher in off-label prescriptions (19.7 per 10 000 person-months) as compared to on-label prescriptions (12.5 per 10 000 person-months).[2]

Although off-label prescribing is legal and common in most countries, physicians carry primary responsibility for accurately prescribing and monitoring therapy with off-label drugs, as acknowledged by the Medicines Healthcare product Regulatory Agency (MHRA) and the General Medical Council (GMC) in the United Kingdom (UK).[4,5] Several studies reported on the inadequate awareness of off-label drugs by physicians and patients. In a survey among 600 physicians in the US, 45% was unaware of the FDA status of the medications they prescribed.[6] In a teaching hospital in India, two-thirds of the residents had insufficient knowledge on unlicensed drugs, and one-third assumed that off-label prescribing was not legal.[7]

The use of off-label drugs seems to vary between different fields of medicine. In the intensive care unit and paediatrics, off-label prescription rates were up to 36% and 62%, respectively.[8,9] In oncology, off-label drug prescriptions were in the range of 18%-41% for hospitalised cancer patients and 7%-50% for ambulatory care patients.[10] In the largest cohort study among office-based physicians, an estimated 21% of overall prescriptions (725 million) were off-label.[11]

In the treatment of inflammatory bowel diseases (IBD), off-label drugs are prescribed as well, especially in patients who failed standard treatment regimens. The overall magnitude of off-label prescribing for Crohn's disease and ulcerative colitis is unknown. To provide optimal therapeutic care, a better understanding of off-label drug prescriptions in this field is needed. We aimed to assess the proportion and characteristics of off-label prescribing for IBD.

2 | METHODS

2.1 | Study design and population

We performed a retrospective analysis of prospectively collected data from the Dutch IBD Biobank. This is a nationwide biobank in which data and biomaterial of adult IBD patients are routinely collected from all seven Dutch university medical centres in the Netherlands since 2007 (ie Erasmus Medical Centre, Leiden University Medical Centre, Maastricht University Medical Centre, Radboud University Nijmegen Medical Centre, University Medical Centre Groningen, University Medical Centre Utrecht and Amsterdam University Medical Centre (locations VU University Medical Centre and Academical Medical Centre). The Dutch IBD Biobank is part of the Parelsnoer Institute (PSI) (www.parelsnoer.org) and is initiated and maintained by the Initiative on Crohn's and Colitis (ICC) working party from the Netherlands.[12]

All adult patients enrolled in the Dutch IBD Biobank with available data on current and historical drug prescriptions for the treatment of IBD were included in the study. Duplications were excluded from the analysis. When it was uncertain whether the unapproved drug was prescribed for IBD or another indication, this prescription was excluded from the off-label analysis as well.

2.2 | Off-label drugs

Drugs which were unlicensed for Crohn's disease and/or ulcerative colitis by the Dutch Medicines Evaluation Board (MEB) were classified as off-label.[13,14] These off-label drugs are depicted in Table 1. Patients with IBD unclassified or IBD indeterminate were included in the ulcerative colitis group, or in case of a re-classification during the disease course, in the group according to the most recent IBD diagnosis. Drugs used in addition to the primary IBD medications, for example supplements or medication for symptom management, were disregarded from the analysis. This also included antibiotics, because we could not identify the precise indications for antibiotic treatment in the nationwide IBD database. In the Netherlands, thioguanine, an alternative thiopurine-derivative, has been conditionally licensed as a certified IBD treatment since mid-2015.[15] Because thioguanine was relicensed recently and solely in the Netherlands, we considered this drug off-label for this study.

2.3 | Data collection

Outcome measures were (a) the proportion of IBD patients exposed to off-label drugs and (b) the rate of off-label drug prescriptions for IBD. Collected data included patient demographics, IBD phenotype according to Montreal classification,[16] disease duration, surgical history, smoking habits and current and historical drug prescriptions for IBD.

2.4 | Statistics

Data were presented as numbers with percentages, means with standard deviations (SD), or medians with interquartile range (IQR), according to their distribution. Demographics and clinical characteristics between off-label users and non-users were compared using the Mann-Whitney *U* test or the independent samples *t* test for continuous variables and the Pearson chi-square test or the Fisher's exact test for categorical variables. Multivariable logistic regression models were built to identify clinical characteristics predictive of increased off-label use, using a backward selection procedure with *p*-removal

set to 0.05. Results of these models are presented with odds ratios (OR) and 95% confidence intervals (CI). Statistical analyses were performed using SPSS Statistics (version 22.0; IBM Corp, Armonk, NY). Two-tailed probability (*P*)-values <0.05 were considered statistically significant.

2.5 | Ethical approval

This study was approved by the ICC PSI-IBD scientific board. All patients included in the Dutch IBD Biobank have given written informed consent.

3 | RESULTS

3.1 | Population characteristics

In April 2018, the Dutch IBD Biobank consisted of 4810 patients. Of these, 227 patients (5%) were excluded due to missing data on historical or current drug records. The remaining 4583 patients with available data on drug records were included in the analysis. A total of 2702 patients (59%) were females, 2826 (62%) had Crohn's disease and 1757 patients (38%) ulcerative colitis. The median age at time of diagnosis was 26 years (IQR 20 - 37) and the median IBD disease duration was 18 years (IQR 11 - 27).

Out of 4583 IBD patients, 1477 (32%) were treated with ≥1 off-label drug(s) for the treatment of Crohn's disease and/or ulcerative colitis. A total of 345 patients (8%) were treated with at least two off-label drugs for IBD. The patient and disease characteristics of the IBD patient population with and without off-label prescriptions for Crohn's disease or ulcerative colitis are depicted in Table 2.

TABLE 1 Overview of off-label drugs used as induction or maintenance treatment for IBD in the Netherlands

Drug name	Class of drug	Off-label in UC	Off-label in CD
Beclomethasone	Steroids	Yes	Yes
Mercaptopurine	Purine-derivative	Yes	Yes
Allopurinol	Purine-derivative	Yes	Yes
Thioguanine	Purine-derivative	Yes[a]	Yes[a]
Cladribine	Purine-derivative	Yes	Yes
Methotrexate	Folate antagonist	Yes	No
Ciclosporin	Calcineurin inhibitor	Yes	Yes
Tacrolimus	Calcineurin inhibitor	Yes	Yes
Mycophenolate	IMPD inhibitor	Yes	Yes
Thalidomide	Thalidomide analogues	Yes	Yes
Tofacitinib	JAK inhibitor	Yes[b]	Yes[b]
Ustekinumab	Biological agent	Yes	No
Golimumab	Biological agent	No	Yes
Certolizumab	Biological agent	Yes	Yes
Natalizumab	Biological agent	Yes	Yes
Rituximab	Biological agent	Yes	Yes
Etanercept	Biological agent	Yes	Yes

CD: Crohn's disease; IBD: inflammatory bowel disease; IMPD: inosine monophosphate dehydrogenase; JAK: Janus kinase; UC: ulcerative colitis.
[a]Thioguanine is licensed for CD and UC conditionally and solely in the Netherlands since April 2015. It was considered off-label for this retrospective analysis.
[b]Tofacitinib is licensed for UC in the Netherlands since July 2018. It was considered off-label for this retrospective analysis.

3.2 | Patient characteristics

There was no difference in gender ratio between patients with (*n* = 1477) and without (*n* = 3106) off-label prescriptions for the treatment of IBD (Table 2). Off-label drug users were slightly older at time of diagnosis (30 ± 13 vs 29 ± 13, $P = 0.019$) and had a shorter median IBD disease duration (16, IQR: 10 - 24 vs 18, IQR: 12 - 27), $P < 0.001$). In addition, patients who never smoked were less exposed to off-label drugs as compared to patients who were previous or current smokers (27% vs 33%, $P < 0.001$). These outcomes were similar for both ulcerative colitis and Crohn's disease.

3.3 | Disease characteristics

Use of off-label drugs was higher in patients with ulcerative colitis compared to Crohn's disease (37% vs 29%, $P < 0.001$). Both for ulcerative colitis and Crohn's disease, there were no phenotypic differences according to the Montreal classification between patients with and without off-label IBD prescriptions. Furthermore, there were no differences in the number of IBD-related surgeries including pouch rates between off-label drug users and non-users. The rates of stoma, however, were higher in the IBD group without off-label drug exposure (10% vs 7%, $P = 0.001$).

3.4 | Off-label drugs

A total of 12 651 historical and current drug records for the induction or maintenance treatment of 4583 IBD patients were available in the database. Of these, 2374 (19%) considered prescriptions which were off-label for Crohn's disease and/or ulcerative colitis. The prevalence of the prescribed off-label drugs for Crohn's disease and ulcerative colitis are summarised in Figure 1.

Overall, the most commonly prescribed off-label drugs for IBD in the whole cohort were mercaptopurine (822/4583, 18%) and beclomethasone (529/4583, 12%). Furthermore, thioguanine was prescribed in 168 (4%) and allopurinol in 149 patients (3%). Methotrexate, an immunomodulator which is only off-label for the treatment of ulcerative colitis, was prescribed in 71 patients (2%).

Other less traditional (non-thiopurine/methotrexate) off-label drugs for the treatment of Crohn's disease or ulcerative colitis were prescribed in 243 patients (6%). The patient and treatment characteristics of this specific group are depicted in Table 3. These off-label immunosuppressant drugs were ciclosporin, prescribed in 105 (2%), tacrolimus in 85 (2%), mycophenolate mofetil in 25 (0.5%) and

TABLE 2 Patient and disease characteristics of 4583 IBD patients

	Patients with off-label drugs	Patients *without* off-label drugs	*P*-value
Number of patients	1477 (32%)	3106 (68%)	
Sex, female	887 (60%)	1815 (58%)	0.30
Age at diagnosis, *yr*	30 ± 13	29 ± 13	0.019
IBD disease duration, *yr*	16 (10-24)	18 (12-27)	<0.001
Smoking *(available data)*	1191 (80%)	2759 (89%)	<0.001
Yes	733 (62%)	1505 (55%)	
No	458 (38%)	1254 (45%)	
Crohn's disease	831 (56%)	1995 (64%)	
Montreal: Age at diagnosis *(available data)*	809 (97%)	1894 (95%)	0.89
<17 (A1)	82 (10%)	213 (11%)	
17-40 (A2)	603 (75%)	1383 (73%)	
>40 (A3)	124 (15%)	298 (16%)	
Montreal: Behaviour *(available data)*	831 (100%)	1995 (100%)	0.94
Non-stricturing, non-penetrating (B1)	487 (59%)	1133 (57%)	
Stricturing (B2)	216 (26%)	545 (27%)	
Penetrating (B3)	128 (15%)	317 (16%)	
Perianal disease (+P)	224 (27%)	511 (26%)	0.27
Montreal: Location *(available data)*	667 (80%)	1490 (75%)	0.55
Ileal (L1)	139 (21%)	338 (23%)	
Colonic (L2)	206 (31%)	447 (30%)	
Ileocolonic (L3)	259 (39%)	546 (37%)	
Upper GI-disease (+L4)	63 (9%)	159 (11%)	
Ulcerative colitis	646 (44%)	1111 (36%)	
Montreal: Extent *(available data)*	483 (75%)	814 (73%)	0.29
Proctitis (E1)	80 (16%)	151 (19%)	
Left-sided (E2)	134 (28%)	246 (30%)	
Pancolitis (E3)	269 (56%)	417 (51%)	
Resection	311 (21%)	611 (20%)	0.28
Small bowel	135 (43%)	283 (46%)	
Large bowel	114 (37%)	179 (29%)	
Small and large bowels	59 (19%)	142 (23%)	
Pouch	59 (4%)	108 (3%)	0.38
Stoma	107 (7%)	314 (10%)	0.001
Multiple drug use (≥5)	968 (66%)	682 (22%)	<0.001

IBD: inflammatory bowel disease; GI: gastrointestinal; yr: year.

thalidomide in 12 IBD patients (0.2%). Off-label targeted immunomodulators, ie biological agents or Janus kinase (JAK) inhibitors, were prescribed in 45 Crohn's disease patients and included certolizumab in 21 (0.5%), golimumab in 15 (0.3%), natalizumab in six (0.1%) and tofacitinib in two patients (0.04%). Furthermore, two patients (0.04%) with ulcerative colitis received off-label treatment with ustekinumab.

If we considered mercaptopurine as the standard of care and on-label for IBD, in line with the international guidelines, the population that received ≥1 off-label drug(s) decreased to 984 patients (984/4583, 21%). The rate of off-label prescriptions for IBD decreased to 1512 out of 12 651 prescriptions (12%).

3.5 | Multiple drug use (≥ 5) during IBD course

Patients who used multiple drugs during their IBD disease course, defined as at least five different drugs, were more likely to receive off-label drugs (66% vs 22%, $P < 0.001$). This association appeared to be stronger in ulcerative colitis (69% of patients with multiple drug use were treated with off-label drugs) than in Crohn's disease

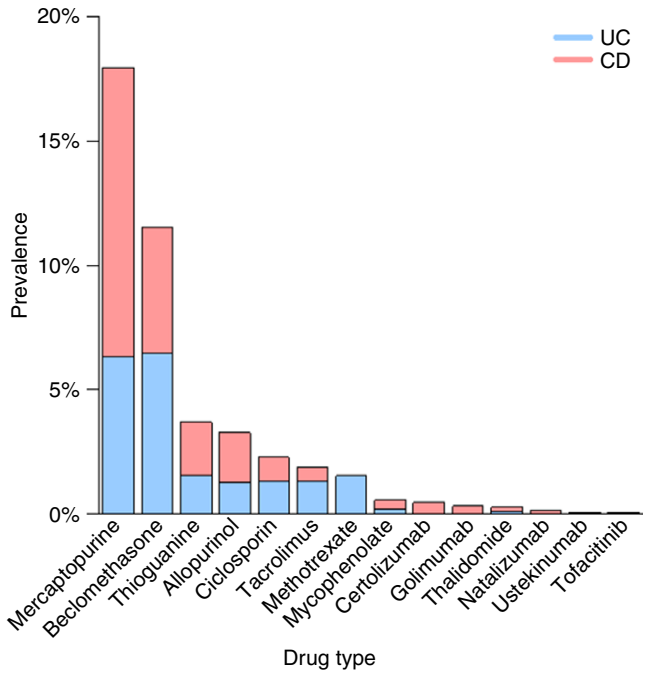

FIGURE 1 Prevalence rates of off-label drug use in Crohn's disease and ulcerative colitis (n = 4583). Bar chart shows the prevalence of prescriptions per each off-label drug among the inflammatory bowel disease population (n = 4583). Prevalence rates of each bar are split into ulcerative colitis (UC) and Crohn's disease (CD)

(53% of patients with multiple drug use were treated with off-label drugs).

3.6 | Determinants of off-label prescribing

Several determinants were associated with increased off-label prescribing as presented in Table 4. Being diagnosed with ulcerative colitis (OR: 1.54, 95 CI%: 1.30-1.82), smoking (OR 0.80, 95 CI%: 0.68-0.94), shorter IBD disease duration (OR: 0.99, 95 CI%: 0.98-0.99), bowel resection (OR: 0.77, 95 CI%: 0.64-0.94) and exposure to ≥ 5 types of drugs during the disease course (OR: 0.15, 95 CI%: 0.13-0.18) were predictive of off-label drug exposure. Age at diagnosis and having a stoma were not predictive for off-label drug use any more in this multivariable model. Gender and other specific disease characteristics, such as IBD phenotype and having a pouch, were again not associated with off-label drug use.

4 | DISCUSSION

In this nationwide IBD cohort of all Dutch university hospitals, 32% of patients were exposed to off-label drugs and 19% of all prescriptions were off-label. Patients with ulcerative colitis were more likely to receive off-label drugs compared to patients with Crohn's disease. Off-label prescriptions were also more common among smokers (in both Crohn's disease and ulcerative colitis) and patients who received at least 5 different drugs for IBD during their disease course. Age at diagnosis and having a stoma were only associated with off-label drugs in the univariate analyses.

Off-label prescribing is encountered across various fields of medicine. Unlike FDA or EMA labelled drugs, off-label drugs may lack scientific evidence and be associated with safety risks considering that they are under-evaluated for the unapproved indication.[2] Accountable use of (off-label) medicines has received growing attention in recent years. Also in the Netherlands, regulations for off-label prescriptions are more strictly regulated by the Dutch Medicines Act since 2007 due to safety concerns.[17] The regulations of off-label prescribing are not harmonised across the world. Even in Europe, each country has established its own regulations.[18] Comparing results on off-label prescribing between countries is therefore difficult, but the need of better understanding and proper prescribing of off-label drugs has been universally acknowledged.

In this Dutch cohort, mercaptopurine was the most frequently prescribed off-label drug for IBD. Although not formally approved in the Netherlands, mercaptopurine is a globally established treatment option for IBD. Compared to most off-label drugs which lack extensive clinical evidence for its use, toxicity and benefit of mercaptopurine for IBD have been broadly studied. Azathioprine, on the other hand, has been a certified IBD treatment option in the Netherlands, but it is not superior to mercaptopurine in literature.[19,20] Hence off-label drugs are not necessarily associated with shortage of scientific evidence as compared with licensed drugs and may be even considered as standard of care. In case that mercaptopurine was recognised as an on-label drug for IBD in the Netherlands, the proportion of patients receiving off-label drugs and the rate of off-label prescriptions in this population would have decreased to 21% and 12%, respectively.

Thioguanine, a less-established thiopurine-derivative, was prescribed in 4% of all patients in this cohort. After being utilised as an off-label drug for IBD for years, thioguanine has been recently licensed conditionally for IBD in the Netherlands.[15] The relicensing of thioguanine was considered unique and important to accomplish safe application of this drug in IBD patients who previously failed azathioprine or mercaptopurine. Prospective registry studies are ongoing to gather additional data on efficacy and safety of thioguanine as a maintenance treatment for IBD before final evaluation.[21] Other frequently prescribed off-label drugs in this IBD cohort included beclomethasone (12%), ciclosporin (2%) and tacrolimus (2%). Also considering these drugs, robust safety databases might be important to adequately determine the benefit-risk profile of these off-label therapies for the treatment of patients with IBD.

We observed a total rate of 19% off-label prescriptions for IBD in this nationwide cohort. This proportion is consistent with the largest cohort study of Radley et al[11] in which an estimated 21% of overall prescriptions (725 million) written by office-based physicians were off-label. In both their and our study, off-label prescriptions did not include use of drugs through an unapproved route of administration, dosage or treatment duration. A wider definition of off-label drug use may have increased the proportion of off-label drug use in

TABLE 3 IBD patients treated with off-label, non-conventional immunomodulating drugs

	Ciclosporin	Tacrolimus	Mycophenolate	Thalidomide	Certolizumab	Golimumab	Natalizumab	Tofacitinib	Ustekinumab
Total N of patients	105	85	25	12	21	15	6	2	2
Crohn's disease	45 (43%)	26 (31%)	16 (64%)	9 (75%)	21 (100%)	15 (100%)	6 (100%)	2 (100%)	
Sex, female	33 (73%)	18 (69%)	11 (69%)	7 (78%)	18 (86%)	10 (67%)	6 (100%)	2 (100%)	
Age at diagnosis, *yr*	26 ± 9	29 ± 14	28 (15 - 72)	27 (11 - 60)	22 (14 - 31)	26 (14 - 50)	25 (20 - 34)	13 (9 - 17)	
IBD disease duration, yr	25 (6 - 54)	14 (6 - 38)	23 (4 - 39)	26 (13 - 54)	19 (3 - 40)	15 (3 - 30)	22 (12 - 27)	26 (17 - 34)1	
Treatment duration, mo.	4 (1 - 38)	5 (1 - 24)	11 (3 - 38)	7 (2 - 80)	16 (12 - 32)	23 (3 - 60)	69 (60 - 78)	20 (15 - 24)	
Resection	9 (20%)	8 (31%)	13 (81%)	4 (44%)	12 (57%)	8 (53%)	1 (17%)	0 (0%)	
Multiple drug use (≥5)	39 (87%)	25 (96%)	16 (100%)	9 (100%)	19 (91%)	9 (60%)	6 (100%)	2 (100%)	
Montreal: Age at diagnosis									
<17 (A1)	4 (9%)	3 (11%)	1 (6%)	3 (33%)	3 (14%)	2 (13%)	6 (100%)	1 (50%)	
17-40 (A2)	37 (82%)	18 (69%)	12 (75%)	5 (56%)	17 (81%)	10 (67%)	0 (0%)	1 (50%)	
>40 (A3)	4 (9%)	5 (19%)	3 (19%)	1 (11%)	1 (5%)	3 (20%)	0 (0%)	0 (0%)	
Montreal: Behaviour									
Non-stricturing, non-penetrating (B1)	26 (58%)	17 (65%)	8 (50%)	5 (56%)	11 (52%)	10 (67%)	0 (0%)	0 (0%)	
Stricturing (B2)	9 (20%)	1 (4%)	5 (31%)	2 (22%)	4 (19%)	3 (20%)	4 (67%)	1 (50%)	
Penetrating (B3)	10 (22%)	8 (31%)	3 (19%)	2 (22%)	6 (29%)	2 (13%)	2 (33%)	1 (50%)	
Perianal disease (+P)	15 (33%)	8 (31%)	7 (44%)	3 (33%)	12 (57%)	5 (33%)	6 (100%)	1 (50%)	
Montreal: Location									
Ileal (L1)	4 (10%)	2 (10%)	1 (6%)	1 (11%)	4 (19%)	2 (13%)	0 (0%)	0 (0%)	
Colonic (L2)	11 (28%)	6 (30%)	3 (19%)	2 (22%)	4 (19%)	2 (13%)	3 (50%)	1 (50%)	
Ileocolonic (L3)	22 (56%)	11 (55%)	12 (75%)	5 (56%)	11 (52%)	9 (60%)	2 (33%)	1 (50%)	
Upper GI-disease (+L4)	3 (8%)	1 (5%)	0 (0%)	1 (11%)	2 (10%)	0 (0%)	1 (17%)	0 (0%)	
Ulcerative colitis	60 (57%)	59 (69%)	9 (36%)	3 (25%)					2 (100%)
Sex, female	30 (50%)	37 (63%)	5 (56%)	0 (0%)					2 (100%)
Age at diagnosis, *yr*	29 ± 12	35 ± 15	17 (9-59)	47 (32-61)					62 (55-68)
IBD disease duration, *yr*	17 (6-54)	14 (2-51)	13 (7-38)	15 (10-20)					5 (4-6)
Treatment duration, *mo.*	5 (1-38)	6 (1-32)	12 (3-244)	NA					32 (11-53)
Resection	11 (18%)	11 (19%)	2 (22%)	0 (0%)					0 (0%)
Multiple drug use (≥5)	48 (80%)	47 (80%)	9 (100%)	2 (67%)					2 (100%)
Montreal: Extent									
Proctitis (E1)	3 (6%)	14 (29%)	0 (0%)	0 (0%)					0 (0%)
Left-sided (E2)	17 (36%)	10 (20%)	3 (33%)	0 (0%)					2 (100%)
Pancolitis (E3)	27 (58%)	25 (51%)	6 (67%)	3 (100%)					0 (0%)

IBD: inflammatory bowel disease; GI: gastrointestinal; mo: months; NA: not available; yr: year.

TABLE 4 Predictive factors for off-label drug use in IBD patients

Determinants	OR	95% CI	*P*-value
IBD disease duration (per year)	0.99	0.98 - 0.99	<0.001
IBD diagnosis			
Crohn's disease	1		
Ulcerative colitis	1.54	1.30 - 1.82	<0.001
Smoking			
Yes	1		
No	0.80	0.68 - 0.94	0.007
Resection			
Yes	1		
No	0.77	0.64 - 0.94	0.011
Multiple drug use (≥5)			
Yes	1		
No	0.15	0.13 - 0.18	<0.001

CI: confidence intervals; IBD: inflammatory bowel disease; OR: odds ratio.

our cohort, however, we were unable to account for these drug characteristics. In the field of paediatrics, off-label prescription rates are considerable higher and rates go up to 80%.[22] Including the paediatric IBD population to our cohort would most likely have increased the proportion of off-label prescriptions substantially.

In this study, we explored a poorly studied aspect of therapeutic IBD care using a nationwide database to provide an insight into off-label prescribing for IBD. Our tertiary care population represents patients with complicated diseases who may have been at increased risk for being treated with drugs outside of the standard treatment regimen. Therefore, generalisation of these findings to the broader IBD population is not prudent. Another limitation of our study was that we strongly depend on the strength of data documentation at the site level. The information in the Dutch IBD Biobank is updated regularly (ie data are automatically uploaded from the local database to the central database at least once a month), still missing data or information bias might have been introduced in our study.[12] Moreover, we only investigated the prevalence of off-label IBD prescriptions and the proportion of patients exposed to these drugs, but we were not able to assess further questions about the reasons for initiation and withdrawal of off-label drugs. Future research is needed to evaluate the considerations for, and knowledge about, off-label prescriptions and its safety and consequences for the treatment of IBD. Another interesting issue would be the impact of costs of off-label prescriptions, as compared to novel costly pharmaceutical agents, on the treatment of IBD.

In conclusion, in a nationwide cohort consisting of tertiary IBD patients, about one-third was exposed to off-label drugs and one-fifth of all IBD prescriptions were off-label. Off-label drug use was more common among patients with ulcerative colitis, smokers and patients who previously received at least five different IBD drugs during their disease course.

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CONFLICTS OF INTEREST

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AUTHORSHIP

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Author contributions: Nanne K. H. de Boer, Cyriel Y. Ponsioen, C. Janneke van der Woude, Andrea E. van der Meulen, Marieke Pierik, Frank Hoentjen, Gerard Dijkstra and Bas Oldenburg enrolled the IBD patients, collected the patient data and critically revised the manuscript. Melek Simsek, Milou L. M. van Riswijk and Sander Verschuren gathered all data. Melek Simsek and Birgit I. Lissenberg-Witte interpreted the data and performed statistical analyses. Melek Simsek prepared the first draft of the article. All authors approved the final version of the manuscript.

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