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ORIGINAL RESEARCH

Real-World Treatment Patterns and Healthcare Resource Use for Ulcerative Colitis and Crohn's Disease in Italy

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ABSTRACT

Introduction: Real-world data are used to inform decision-makers and optimise therapeutic management for patients with ulcerative colitis (UC) and Crohn's disease (CD). We analysed data on the epidemiology (by using proxies of prevalence and incidence), patient characteristics, treatment patterns and associated healthcare direct costs for the management of patients with UC and patients with CD in Italy.

Methods: This retrospective observational study used administrative databases from eight Local Health Units geographically distributed across Italy. Adult patients with a hospitalisation and/or an exemption for UC or CD were included. Study outcomes were summarised descriptively, and limited statistical tests were performed.

Results: At baseline, 9255 adults with UC and 4747 adults with CD were included. Mean (standard deviation) age at inclusion was 54.0 (18.4)/48.6 (18.1) years, for UC/CD. The estimated average incidence of UC and CD for the period 2013–2020 was 36.5 and 18.7 per 100,000, respectively. The most frequently prescribed drug category for patients with UC/CD was conventional treatment [mesalazine and topical corticosteroids (67.4%/61.1%), immunomodulators and systemic corticosteroids (43.2%/47.7%)], followed by biologic treatments (2.1%/5.1%). The mean annual total direct cost per patient was 7678 euro (€), for UC and €6925 for CD.

Conclusion: This analysis, carried-out in an Italian clinical setting, may help to optimise therapy for patients with UC and CD and provide relevant clinical practice data to inform decision-makers.

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PLAIN LANGUAGE SUMMARY

Data from clinical practice can be used to guide healthcare decisions and optimise treatment for patients with ulcerative colitis and Crohn's disease. This study used anonymised patient information from almost four million individuals across Italy to describe the epidemiology, patient characteristics, treatment patterns and healthcare costs of patients with ulcerative colitis and Crohn's disease. Adults with an Italian National Health System code in their records associated with the diagnosis of ulcerative colitis or Crohn's disease were included. Baseline characteristics were balanced between groups and rates of perceived incidence were numerically similar to the results reported in similar Italian studies. This study found that patients with ulcerative colitis and Crohn's disease were most often prescribed conventional treatments, and biological treatments were least-commonly prescribed. More than half of patients with ulcerative colitis and nearly half of those with Crohn's disease were persistent with first (index) treatment of mesalazine and topical corticosteroids and with biologic index treatment during the follow-up period. Switch occurred in up to approximately a quarter of patients with ulcerative colitis and Crohn's disease. The main factors that predicted switch were index biologic for ulcerative colitis and baseline comorbidities for Crohn's disease. The average direct cost per patient in 1 year was 7678 euro (€) for ulcerative colitis and €6925 for Crohn's disease. The results of this analysis may help to optimise therapy for patients with ulcerative colitis and Crohn's disease, and to inform decision-makers in healthcare systems on which treatment options provide value for money and benefit patients.

Keywords: Healthcare cost; Inflammatory bowel disease; Real-world evidence; Therapeutics

Key Summary Points

Ulcerative colitis (UC) and Crohn's Disease (CD) are chronic relapsing and debilitation conditions. This database study utilised real-world evidence from adults with a hospitalisation and/or exemption for UC and CD in Italy.

This study described the epidemiology (by using proxies of incidence and prevalence), treatment approaches, patient characteristics and associated healthcare costs of patients with UC and CD.

Conventional treatments (mesalazine and topical corticosteroids; immunomodulators and systemic corticosteroids) were more frequently prescribed than biologic agents for the treatment of ulcerative colitis and Crohn's disease despite patients meeting the eligibility criteria for biologic treatment.

These results may support the optimisation of treatment options for patients with UC and CD and build upon existing evidence to inform healthcare policy makers.

INTRODUCTION

Inflammatory bowel disease (IBD) comprises ulcerative colitis (UC) and Crohn's disease (CD), both of which are chronic, relapsing and debilitating conditions with a disease course that may range in severity and progression [1–3]. In Italy, the prevalence of IBD was estimated at 0.26% (264 per 100,000 population on 1 January 2019), based on projections using real-world data from northern Italy [4].

The onset of both UC and CD is usually in young adulthood [2, 3]. UC is characterised by mucosal inflammation that primarily affects the colonic mucosa in a continuous way, whereas

patchy (discontinuous) transmural inflammation affecting both the small and large bowel is typical for CD [1]. Several comorbidities have been proposed to be related to IBD, including psoriasis, osteoporosis, anxiety and depression [5–10].

Recent treatment guidelines from the European Crohn's and Colitis Organisation (ECCO) and the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) include a range of therapeutic options for IBD. Recommendations include conventional medications (aminosalicylates, corticosteroids, immunomodulators), and biologics, such as monoclonal antibodies blocking tumour necrosis factor (TNF) alpha (infliximab, adalimumab, golimumab) and against integrins (vedolizumab) or interleukins (ustekinumab), or small molecules, such as JAK inhibitors (tofacitinib) [11–14].

Current treatment goals for adults with IBD, from the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) initiative, include symptomatic/clinical response and remission, and normalisation of C-reactive protein (a biomarker of inflammation) as immediate and short-term treatment targets. Normalisation of faecal calprotectin is included as an intermediate target, and endoscopic healing, absence of disability and normalised health-related quality of life (HR-QoL) as long-term targets [15]. Rectal bleeding, bowel urgency and increased stool frequency are important symptoms to target in UC, and abdominal pain and increased stool frequency are key symptoms in CD [15–17]. To optimise therapeutic management for patients with UC and CD, and to inform decision-makers, it is important to understand patient characteristics, treatment patterns, healthcare resource use and costs associated with IBD. This study aimed to estimate the epidemiology of UC and CD in a real-world setting in Italy (by proxying prevalence and incidence), and to describe demographic characteristics of patients with these conditions, as well as the treatment management of patients with UC and CD including patterns of persistence and switch, associated healthcare resource use and direct costs covered by the Italian National Health System (INHS).

METHODS

Study Design, Data Sources and Population

A retrospective observational study using secondary data collected from administrative databases from eight Local Health Units (LHUs), covering health-assisted individuals (beneficiaries). Administrative databases among the INHS contain stored data for the reimbursement of healthcare services.

In Italy, healthcare is provided to all citizens and residents by a mixed public–private system. The public system is administered on a regional basis, each region is divided into LHUs [18]—administrative bodies that are responsible for delivering health services in the broader community. These services include hospitalisations and outpatient specialist visits/diagnostic tests provided by the public hospitals (hospital centres or university hospitals) or by contracted private hospitals, reimbursed by their respective LHUs. For this study, the respective LHUs were selected by geographical distribution, data completeness and high-quality linked datasets.

Pre-existing anonymous univocal numeric codes associated with each patient enabled the electronic linkage of all the patients' records across five databases (Table S1). The integration of all administrative datasets allowed one to represent the patient's entire clinical history.

Adult patients (≥ 18 years of age) within the INHS with a diagnosis of UC or CD between January 2013 and December 2020 (inclusion/enrolment period) were included. The diagnosis of UC or CD was identified by the presence of at least one record of hospitalisation (inpatient setting) that included a discharge diagnosis at any level of UC (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 556.x) or CD (ICD-9-CM code 555.x) [19], or an exemption code (009.556 or 009.555, specific for UC and CD, respectively) (outpatient setting) from the INHS indicating a diagnosis of one of these chronic diseases.

The retrospective analysis of administrative databases involved secondary data extraction, and local ethics committees of each of the

participating LHUs approved the study as per Agenzia Italiana del Farmaco (AIFA) guidelines and Italian law. Details of the local ethics committee including name, protocol code and date of protocol approval are as follows: "Comitato etico interprovinciale Area I", Protocol 68/CE/20, approval date 3/12/2020; "Comitato Indipendente di Etica Medica", Protocol 48,148, approval date 28/05/2021; "Comitato etico interprovinciale Area I", Protocol 10/CE/22, approval date 31/01/2022; "Comitato Etico Lazio 2", Protocol 0031401/2022, approval date 09/02/2022; "Comitato Indipendente di Etica Medica", Protocol 48,144, approval date 28/05/2021; "Comitato Etico per la Sperimentazione Clinica della provincia di Venezia e IRCCS S. Camillo", Protocol 1405/AULSS 3 Mestre, approval date 26/10/2021; "Comitato Etico Regionale dell'Umbria", Protocol 19,414/20/ON, approval date 27/10/2021; "Comitato Etico Interaziendale A.O. SS. Antonio e Biagio e Cesare Arrigo – Alessandria", Protocol AslVC.FarmT.21.02, approval date 16/12/2021. The study was conducted in compliance with ethical principles based on the Declaration of Helsinki and consistent with Good Pharmacoepidemiology Practices and applicable laws and regulations of Italy. All patient data collected were anonymised to ensure confidentiality and privacy. The anonymous univocal numeric code ensured total compliance with the European General Data Protection Regulation (GDPR) (2016/679). The results are exclusively in aggregated form and not attributable to a single institution, department, doctor, individual or individual prescribing behaviours. On the basis of the Data Privacy Guarantor Authority (General Authorisation for personal data treatment for scientific research purposes – n.9/2014), informed consent was not required, as its collection would be impossible for organisational reasons.

The index date for the analysis was defined as the first diagnosis of UC or CD (first hospitalisation or exemption code) during the inclusion period. Data were also collected for a characterisation period, defined as at least a 1-year period prior to the index date, and for a follow-up period of at least 1 year, defined as the period of observation from the index date until the end of the study or until death. Therefore, the overall period of data collection in the study ranged from January 2012 to December 2021. Patients who were transferred to a different LHU during the study period were excluded. In addition, a minimum characterisation and follow-up period of 1 year was required for inclusion.

Study Outcomes

Study outcomes included (i) proxy of prevalence and incidence of UC and CD at index date; (ii) baseline demographic at index date; (iii) treatment patterns at index date (index treatment) and during follow-up; and (iv) healthcare resource use and associated direct costs for the INHS during follow-up.

For all patients included in the study, gender and age were recorded at inclusion. Comorbidities at baseline were evaluated using the Charlson Comorbidity Index (CCI) [20], assigning a score to each comorbidity category (assessed during the previous 12 months, by evaluating drug treatment and hospitalisations). The index score represents the sum of the weights for all identified conditions.

The demographic features were collected at baseline and during the characterisation period according to hospital admissions and prescribed drugs at least 1 year prior to the index date. Comorbidity definitions based on Vadstrup et al. (2020) [21] are included in Table S2.

Treatments included in the analysis were categorised as (i) conventional treatments (mesalazine and topical corticosteroids; immunomodulators and systemic corticosteroids); and (ii) biologic treatments. Details of treatments included in each category are provided in Table S3.

With respect to treatment patterns, the following definitions were used:

- Switch: During the follow-up period a different drug was prescribed other than that administered at the index date.
- Discontinuation: Index treatment was stopped, and no other drug was prescribed for the condition during the follow-up period, or a switch was made.

- Persistence: No treatment change (switch or discontinuation) occurred by the end of the follow-up period (last trimester).
- Add-on: In addition to the index treatment, another drug was also prescribed before the end of the follow-up period.
- Dose escalation/de-escalation: Two consecutive prescriptions with an average weekly dose 30% [22] greater or lower than the initial average weekly maintenance dose (post-induction phase) for biologic treatments.
- Duration of treatment: The time between the first prescription for the index treatment and either the end of the index treatment or the end of follow-up, whichever was earliest.

Regarding healthcare resource use and costs, overall direct medical costs in euro (€) were derived from resource-use data for drug treatments, hospitalisation and outpatient specialised services, and calculated on the basis of the price reimbursed by the INHS in the year they occurred. Cost values more than three standard deviation (SD) points from the mean were excluded as potential outliers.

Analysis

Study variables were summarised descriptively, which was considered appropriate for the retrospective longitudinal study design. A sensitivity analysis on incidence rates for the respective IBDs was performed, excluding years 2013, 2014 and 2017, which were affected by an overestimation of patients due to administrative reasons. Analyses were also conducted for patients with UC and for those with CD stratified and allocated to subgroups based on IBD drug treatment at baseline. Multivariate regression models were used to evaluate predictors of persistence to biologic first (index) treatment and switch to another biologic among the baseline variables, by controlling any variables evaluated at baseline. Thus, the association of treatment switch and baseline variables was evaluated by a Cox regression multivariate approach (reported as odds ratio [OR]; 95% confidence interval [CI]) considering the following covariates: index treatment, age at index date, gender, CCI, and comorbidities assessed at baseline (hypertension, dyslipidaemia, diabetes, chronic obstructive pulmonary disease, depression, cerebrovascular diseases, ankylosing spondylitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, systemic lupus erythematosus). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Overall Cohorts of Patients with UC and CD

Proxy for Prevalence and Incidence of IBD and Baseline Demographic Characteristics

Among the total population of 3.8 million INHS beneficiaries in the catchment area of the eight Italian LHUs, 9255 adults with a diagnosis of UC and 4747 adults with CD met the inclusion criteria of the study.

The analysis showed that the prevalence of UC, calculated for 31 December 2020, was 269.4 per 100,000 beneficiaries (302.1 for men and 238.4 for women) and for CD it was 141.3 per 100,000 beneficiaries (151.9 and 131.2, respectively, for men and women).

The estimated average incidence of UC, based on the overall inclusion criteria, for the period 2018 to 2020 was 20.2 per 100,000 beneficiaries and ranged between 11.1 and 25.0 per 100,000 beneficiaries.

The estimated average incidence of CD, based on the overall inclusion criteria, for the period 2018 to 2020 was 11.5 per 100,000 beneficiaries and ranged between 5.7 and 14.9 per 100,000 beneficiaries.

Considering baseline demographics characteristics of patients with UC, the mean (SD) age at inclusion (index date) was 54.0 (18.4) years, 55.1% were male, and the mean (SD) CCI was 0.6 (1.1) with a median (interquartile range [IQR]) value of 0.0 (0.0–1.0). Patients with CD were numerically younger (48.6 years; SD 18.1) and more evenly split between genders (52.2% male) than those with UC, although the CCI was similar between these IBD cohorts (Table 1). During the characterisation period, the most common comorbidities observed for patients

Table 1 Patient demographic and clinical characteristics

Parameter	Condition	
	Ulcerative colitis (UC)	Crohn's disease (CD)
Number of patients	9255	4747
Age (years) at index date, mean (SD)	54.0 (18.4)	48.6 (18.1)
Age (years) at index date, median (IQR)	54.0 (40.0–68.0)	47.0 (34.0–62.0)
Male gender, %	55.1	52.2
Duration of disease from diagnosis to index date, mean number of years (SD)	2.0 (4.4)	1.5 (3.5)
Duration of disease from diagnosis to index date, median number of years (IQR)	0 (0–1)	0 (0–1)
Charlson Comorbidity Index, mean (SD)	0.6 (1.1)	0.5 (1.0)
Charlson Comorbidity Index, median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Most common comorbidities[a], %		
Hypertension	36.6	29.0
COPD	19.6	18.6
Dyslipidaemia	17.5	12.1
Diabetes	9.9	6.3
Depression	9.5	9.9
Cerebrovascular disease	6.7	4.2
Treatment prior to enrolment[b], %		
Conventional treatments		
Mesalazine and topical corticosteroids	67.4	61.1
Immunomodulators and systemic corticosteroids	43.2	47.7
Biologics	2.1	5.1
Received ≥ 1 treatment	78.7	75.9
Hospitalisation prior to enrolment[c], %		
Digestive system	17.9	25.0
Circulatory system	7.8	4.9
Musculoskeletal system and connective tissue	6.0	6.1
Respiratory system	3.7	2.5
Nervous system	3.6	2.5
Kidney and urinary tract	3.1	3.2
Hepatobiliary system and pancreas	3.0	3.0
Skin, subcutaneous tissue and breast	2.3	2.3
Pregnancy, childbirth and puerperium	2.3	2.8
Female reproductive system	1.8	2.1

COPD chronic obstructive pulmonary disease, *IQR* interquartile range, *SD* standard deviation

[a]Reported in ≥ 5% of patients with UC and/or CD

[b]During the characterisation period; treatments not mutually exclusive

[c]Most frequent reasons for hospitalisation reported in ≥ 2% of patients with UC and/or CD during the characterisation period

with UC and CD were hypertension (36.6% and 29.0%, respectively), chronic obstructive pulmonary disease (19.6% and 18.6%, respectively) and dyslipidaemia (17.5% and 12.1%, respectively) (Table 1).

Treatment Patterns

Prior to enrolment (i.e. during the characterisation period), more than three-quarters of patients with UC (78.7%) and CD (75.9%) were prescribed at least one IBD-related drug

(Table 1). The most frequently prescribed drug category was conventional treatments: mesalazine and topical corticosteroids prescribed to patients with UC (67.4%) and CD (61.1%) and immunomodulators and systemic corticosteroids prescribed to 43.2% of patients with UC and 47.7% of patients with CD. At baseline, biologic treatments were prescribed to 2.1% and 5.1% of patients with UC and patients with CD respectively. During this period, 17.9% of patients with UC and 25.0% of those with CD had hospitalisation(s) related to the gastrointestinal tract/digestive system (Table 1).

During a mean follow-up (observation) period of 5.1 years (SD 2.6), the proportion of patients with UC who were prescribed drug treatment with at least one therapeutic agent increased to 89.3%, including 10.4% who were prescribed at least one biologic treatment. Mesalazine and topical corticosteroids were prescribed most frequently (80.7%) followed by immunomodulators and systemic corticosteroids (59.3%) (Fig. 1).

Similarly, over a mean follow-up period of 5.3 years (SD 2.6), 88.9% of patients with CD were prescribed one or more IBD-related drug treatments, and the proportion of patients prescribed at least one biologic treatment reached 19.7%. Mesalazine and topical corticosteroids were prescribed most frequently (76.3%) followed by immunomodulators and systemic corticosteroids (63.3%) (Fig. 1).

Details regarding persistence, discontinuation, add-on and switch among patients with IBD receiving first (index) treatment with each of the three previously described drug categories are provided in Table 2. More than half of patients with UC and almost half of those with CD were persistent with index treatment comprising mesalazine and topical corticosteroids and with biologic index treatment during the follow-up period. Fewer than one-quarter of patients with IBD were persistent with immunomodulators as index treatment.

Among the 967 patients (10.4%) with UC who were prescribed a biologic treatment during the follow-up period, adalimumab (38.2%) and infliximab (31.6%) were most prescribed, followed by vedolizumab (14.1%), golimumab (12.8%) and ustekinumab (3.3%). These agents were available in Italy throughout the study follow-up period, aside from vedolizumab, which was first approved for medical use in May 2014 in the European Union. Tofacitinib

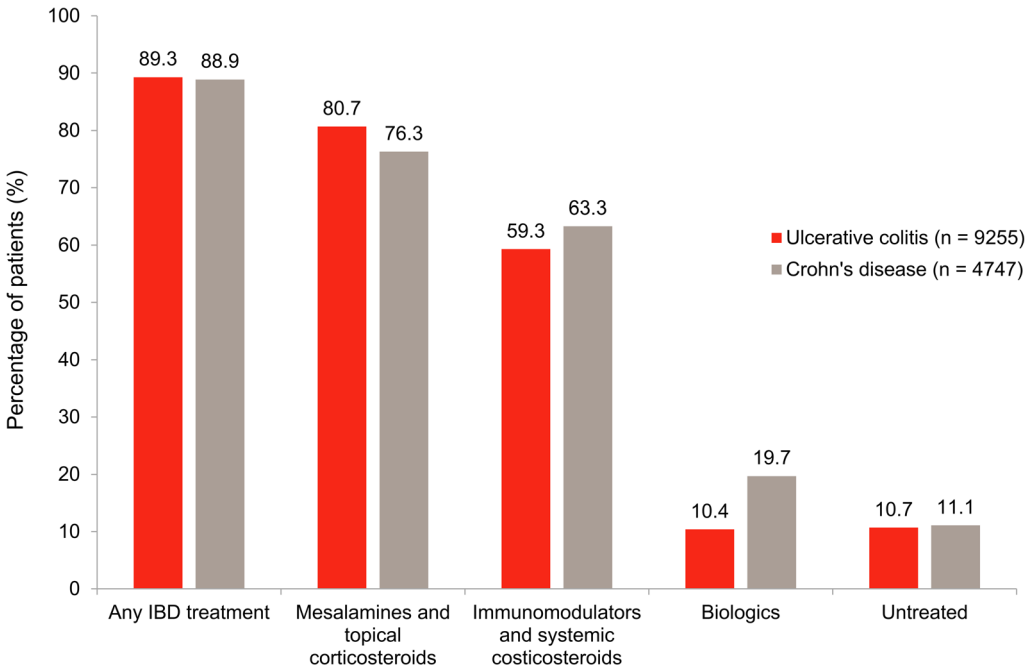


Fig. 1 Treatment during follow-up period. *IBD* inflammatory bowel disease

Table 2 Treatment patterns for patients receiving first (index) treatment during follow-up period

First (index) drug	Switch no. of evaluable patients	Mean (SD) duration of treatment (months)/median (IQR)	Add-on therapy (% of patients)	Switch (% of patients)	Persistence no. of evaluable patients[a]	Persistence[b,c] (% of patients)	Discontinuation[c] (% of patients)
Ulcerative colitis							
Conventional treatments							
Mesalazine and topical corticosteroids	6665	46.6 (33.0)/43.7 (18.4–74.6)	53.2	7.2	6043	53.2	46.8
Immunomodulators and systemic corticosteroids	1464	29.4 (31.4)/18.7 (0.0–50.1)	41.0	7.8	1204	22.4	77.6
Biologics	135	40.4 (28.5)/42.3 (15.0–56.8)	77.8	6.7	132	53.8	46.2
Crohn's disease							
Conventional treatments							
Mesalazine and topical corticosteroids	3029	42.9 (32.9)/39.8 (13.4–69.5)	58.1	8.1	2799	44.6	55.4
Immunomodulators and systemic corticosteroids	999	31.5 (31.2)/24.1 (0.94–53.0)	41.0	10.6	876	21.3	78.7
Biologics	193	44.8 (28.2)/42.7 (21.9–65.2)	68.9	11.4	188	45.7	54.3

IQR interquartile range, *SD* standard deviation

[a]Number of evaluable patients was lower for categories 'persistence' and 'discontinuation' than for other categories

[b]Patients with add-on therapy were considered persistent to index medication; patients who underwent a switch in treatment were not considered persistent

[c]Deaths excluded

was not included in this analysis as it was only reimbursed in Italy from December 2020 and at the time of enrolment fewer than 10 patients were identified receiving tofacitinib treatment.

For the 937 biologic-treated patients (19.7%) with CD, the most prescribed biologic during follow-up was adalimumab (62.3%), followed by infliximab (26.7%), vedolizumab (7.0%) and ustekinumab (3.9%).

Evaluation of treatment patterns for each biologic treatment showed that 16.2–25.2% of patients with UC who were prescribed a biologic were switched to another biologic treatment (Table 3). Among biologic treatments, the mean duration to switch (period between the first (index) biologic prescription and the switch to a different biologic treatment) ranged from 15.0 to 26.6 months. These results exclude ustekinumab, as only 32 patients received this biologic as an index drug. Regarding predictors of switching to another biologic, by controlling baseline variables assessed in the current analysis, index treatment with infliximab versus adalimumab was the only significant baseline variable associated with a significantly increased risk to switch (OR 1.82; 95% CI 1.01–3.30; $P < 0.05$) (Fig. S1). Ustekinumab was not included in these results as fewer than four patients were observed switching. Persistence to biologic index medication ranged from 60.8% to 68.5%, and dose escalation was reported in 6.3–38.5% of patients with UC (including ustekinumab). No baseline variables were identified as predictors of biologic treatment persistence (Fig. S2). Dose escalation was most likely with adalimumab (38.5% of patients), infliximab (30.1%) and vedolizumab (26.5%), and least likely with golimumab (14.5%) and ustekinumab (6.3%) (Table 3).

Switch from biologic index medication to another biologic during the follow-up period occurred in 13.6–23.6% of patients with CD. Among baseline variables, the CCI and presence of hypertension were significant predictors of switching to another biologic (OR 1.29, 95% CI 1.01–1.66 and OR 1.63, 95% CI 1.02–2.60; $P < 0.05$) while the presence of dyslipidaemia significantly decreased the risk to switch (OR 0.39; 95% CI 0.16–0.93; $P < 0.05$) (excluding ustekinumab because of very low patient numbers) (Table 3 and Fig. S1). Persistence to biologic index medication ranged from 65.2% to 78.1%, dyslipidaemia and psoriatic arthritis were significant predictors of treatment persistence (OR 2.41, 95% CI 1.02–5.73 and OR 0.25, 95% CI 0.08–0.80; $P < 0.05$) (Fig. S2). Dose escalation occurred in 18.9–46.6% of patients with CD (including ustekinumab). Dose escalation was most likely with adalimumab (46.6% of patients), followed by infliximab (26.4%) and vedolizumab (25.8%) and was least likely with ustekinumab (18.9%) (Table 3).

Healthcare Resource Use and Direct Costs

Healthcare resource consumption generally decreased during the follow-up period in both IBD cohorts, even though patients who died and outlier values were excluded. Patient numbers were further reduced after the first year because not all patients were followed up beyond the first year (Table 4), which may have affected results. Overall, during the entire follow-up period and for all 9157 patients with UC, the mean (SD) annual number of prescriptions/drugs was 15.5 (16.8), mean (SD) annual number of hospitalisations was 1.3 (15.3), and mean (SD) annual number of outpatient specialist services was 5.4 (8.8). Results were generally similar for patients with CD (Table 4).

The mean/median annual total direct cost per patient with UC was €7678/€1627 and that with €6925/€1991 was CD. The median costs for drugs and hospitalisations accounted for 34–44% and 22–28% of annual total costs per patient, respectively (Fig. 2).

DISCUSSION

This observational study, conducted in Italy from 2013 to 2020, provides real-world data on the proxy of prevalence/incidence, patient characteristics, treatment patterns, healthcare resource use and healthcare direct costs for patients with UC and CD in Italy.

The overall prevalence of UC (269.4 per 100,000 beneficiaries [approx. 0.27%]) and CD (141.3 per 100,000 beneficiaries [approx. 0.14%]) observed on 31 December 2020 in our

Table 3 Treatment patterns for first prescription of each biologic treatment

First biologic	Switch no. of evaluable patients	Switch to different biologic (% of patients)	Mean duration to switch (months)/median (IQR)	Persistence no. of evaluable patients[a]	Persistence to biologic treatment (any agent)[b] (% of patients)	Persistence to index biologic[c] (% of patients)	Interruption to index medication[c] (% of patients)	Dose escalation/de-escalation (% of patients)
Ulcerative colitis								
Adalimumab	369	21.7	26.6/19.7 (8.7–39.3)	345	74.8	67.0	33.0	38.5/27.4
Golimumab	1124	25.0	18.9/13.1 (7.1–26.8)	116	71.6	62.1	37.9	14.5/66.1
Infliximab	306	25.2	20.1/14.2 (6.0–28.3)	286	74.1	60.8	39.2	30.1/14.7
Ustekinumab	32	NR	NR	24	70.8	66.7	33.3	6.3/9.4
Vedolizumab	136	16.2	15.0/12.5 (6.7–19.7)	108	75.9	68.5	31.5	26.5/13.2
Crohn's disease								
Adalimumab	584	18.3	33.7/28. (17.4–49)	543	76.6	74.2	25.8	46.6/27.9
Infliximab	250	23.6	25.1/19.9 (9.1–38.4)	230	72.2	65.2	34.8	26.4/14.8
Ustekinumab	37	NR	NR	32	81.3	78.1	21.9	18.9/0
Vedolizumab	66	13.6	11.0/11.9 (7.1–14.3)	54	81.5	75.9	24.1	25.8/13.6

IQR interquartile range, *NR* not reported for data privacy (very small number of patients in group)

[a]Number of evaluable patients was lower for categories 'persistence' and 'interruption' than for other categories

[b]At least one prescription for any biologic during the last 3 months of 12-month follow-up period

[c]At least one prescription for the specific index biologic during the last 3 months of 12-month follow-up period

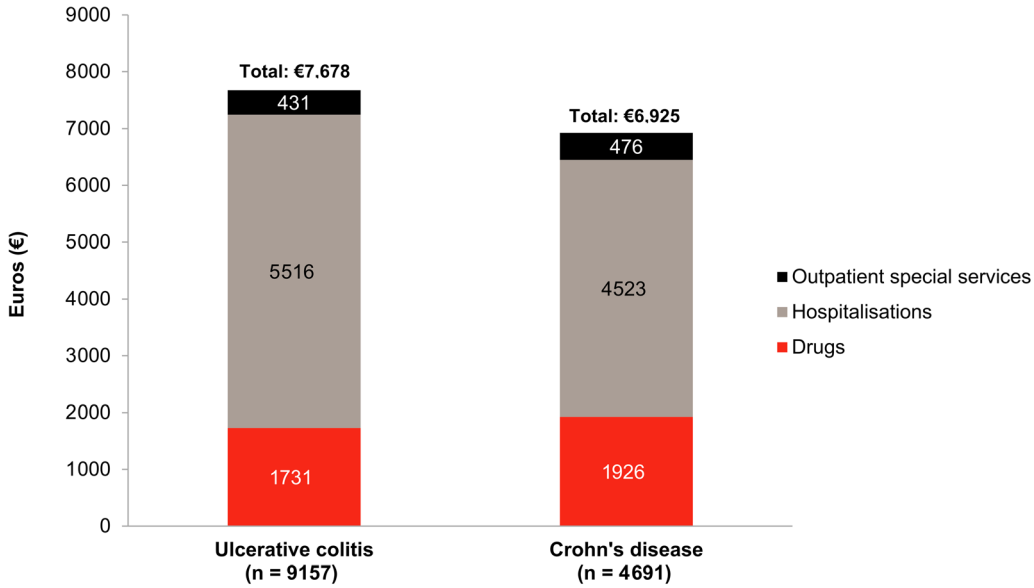
Table 4 Mean (standard deviation) annual healthcare resource use per patient during the follow-up period

Description	Overall follow-up (*n* = 9255)	First year (*n* = 8915)	Second year (*n* = 8046)	Third year (*n* = 7256)
Ulcerative colitis				
Drugs/prescriptions, mean (SD)	15.5 (16.8)	15.4 (12.7)	13.8 (12.1)	13.4 (12.0)
Hospitalisations, mean (SD)	1.3 (15.3)	0.6 (1.0)	0.2 (0.7)	0.2 (0.6)
Outpatient special services (prescriptions), mean (SD)	5.4 (8.8)	5.4 (7.6)	4.9 (7.5)	4.8 (7.7)
Drugs/prescriptions, median (IQR)	11.9 (5.8–20.5)	13.0 (6.0–22.0)	11.0 (5.0–19.0)	11.0 (5.0–18.0)
Hospitalisations, median (IQR)	0.2 (0.0–0.5)	0.0 (0.0–1.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Outpatient special services (prescriptions), median (IQR)	3.4 (1.4–6.8)	3.0 (1.0–7.0)	3.0 (1.0–7.0)	3.0 (1.0–7.0)
Description	**Overall follow-up (*n* = 4747)**	**First year (*n* = 4618)**	**Second year (*n* = 4180)**	**Third year (*n* = 3714)**
Crohn's disease				
Drugs/prescriptions, mean (SD)	14.7 (15.1)	15.2 (12.3)	13.4 (12.0)	13.0 (12.2)
Hospitalisations, mean (SD)	1.1 (10.5)	0.8 (1.1)	0.3 (0.7)	0.2 (0.7)
Outpatient special services (prescriptions), mean (SD)	5.6 (8.5)	5.8 (7.2)	5.2 (7.2)	4.9 (7.3)
Drugs/prescriptions, median (IQR)	11.6 (5.2–19.8)	13.0 (6.0–22.0)	11.0 (4.0–19.0)	11.0 (4.0–19.0)
Hospitalisations, median (IQR)	0.2 (0.0–0.6)	1.0 (0.0–1.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Outpatient special services (prescriptions), median (IQR)	3.6 (1.5–7.1)	4.0 (1.0–8.0)	3.0 (1.0–7.0)	3.0 (1.0–7.0)

IQR interquartile range, *SD* standard deviation

study was generally in line with, albeit numerically higher than, previously reported data from 1 January 2019 in Italy [4]. In that study, which used real-world data from Milan in northern Italy to project results for the Italian population, the expected number of patients with prevalent IBD was 264.0 per 100,000, which included 164.3 and 99.8 per 100,000 for UC and CD, respectively. However, the data from northern Italy showed an age-standardised prevalence rate of 442.7 per 100,000 for IBD, which included 272.9 and 169.8 per 100,000 for UC and CD, respectively [4], and these findings were not substantially different from results of our study. Crocetti et al. (2021) [4] also showed incidence rates of UC (9.3 per 100,000) and CD (15.6 per 100,000), which were numerically lower than our findings.

Considering the baseline characteristics of the included subjects, the mean age of patients with UC and CD in our analysis at the index date was 54.0 and 48.6 years, respectively. This patient population was somewhat older than expected (e.g. compared with the previously



	Ulcerative Colitis	Crohn's Disease
n	**9157**	**4691**
Drug costs (Euro)	712.43	676.92
	(273.10–1566.56)	(198.40–1931.53)
Hospitalisation costs (Euro)	366.4	569.49
	(0.00–1521.52)	(0.00–1860.96)
Outpatient special services costs (Euro)	192.8	228.48
	(70.71–430.13)	(84.78–479.50)
Total costs (Euro)	1626.55	1991.36
	(718.71–4297.64)	(805.06–5235.70)

Fig. 2 Mean annual direct healthcare costs per patient during follow-up (outliers excluded). Data are median (interquartile range)

mentioned study from northern Italy) and this figure could be associated with the adopted definition of UC or CD diagnosis: date of the first hospitalisation or exemption in the data sources might be subsequent to the effective date of disease onset. The older age of included patients also may explain, to some extent, the relatively high rate of comorbidities observed in our study.

While most patients (approx. 89%) received IBD-related treatment during the follow-up period, the proportion of patients receiving biologic agents was relatively low (approx. 10% for UC and approx. 20% for CD). Similar findings were reported in an observational study in an Italian population, which found that 28.6% of patients diagnosed with UC or CD met the eligibility criteria for biologic therapies but were not receiving a biologic treatment [23]. This suggests there may be room for improvement in optimising therapy, enhancing HR-QoL and potentially reducing hospitalisations for these patients. Ustekinumab was the least prescribed biologic at follow-up, representing approximately 3% of patients for both CD and UC. In contrast, a multicentre Italian study by Ferretti et al. (2022) [24] reported that 9% of patients with CD and UC were receiving ustekinumab. This difference could be due to ustekinumab not being introduced in Italy until September 2019 (i.e. towards the end of our observation period), and is generally prescribed as second-line treatment (our study identified the first biologic prescribed). Regarding switch data, the number of patients receiving ustekinumab during the follow-up could increase, since some patients switched from anti-TNF to ustekinumab during the follow-up period.

During the study period, approximately half of patients with IBD were persistent with biologic treatments, and/or conventional treatments such as mesalazine and topical corticosteroids, despite mesalazine not being recommended as appropriate treatment for CD since 2007 [25]. Less than one-quarter of patients with IBD were persistent with immunomodulators and systemic corticosteroids. Predictors of persistence to biologic index treatment among baseline variables for CD were dyslipidaemia and psoriatic arthritis, while no significant predictors were identified for UC. Index treatment with infliximab (UC), CCI and hypertension (CD) were associated with switch to another biologic. Studies by Jung et al. (2020) [26] and Chen et al. (2019) [27] previously investigated predictors of non-persistence and switch, baseline variables considered differed from those included in our study, apart from index biologic and gender. Both studies reported steroid use at biologic initiation and was significantly associated with increased risk of non-persistence and switch in both UC and CD. Similarly, Chen et al. (2019) [27] also reported steroid treatment as a significant predictor of non-persistence in IBD. Jung et al. (2020) [26] and Chen et al. (2019) [27] reported significant impacts on switch (being male, adalimumab user over infliximab user) and non-persistence (being male, golimumab user over infliximab user) in IBD. Being male was significantly associated with increased risk of switch in UC and decreased risk of non-persistence CD [26]. Conversely, Chen et al. (2019) [27] reported being female was significantly associated with increased risk of non-persistence in IBD. Variability between these findings and our study could be explained by the differences in baseline variables considered. Dose escalation of biologic treatments was also undertaken for a substantial proportion of patients with UC and CD.

In this study, during the first year of follow-up, the mean annual direct costs per patient were €7678 up to €4298 for patients with UC (median €1627 [IQR 719–4298]) and €6925 up to €5236 for those with CD (median €1991 [IQR 805–5236]), with most of the cost (approx. 65–70%) attributed to hospitalisations. Burisch et al. (2020) [28] reported an increase in costs for biologics and a decrease in costs associated with conventional medications, hospitalisations and surgeries over a 5-year follow-up period from diagnosis in a European population. Hospitalisation and diagnostic procedures accounted for more than 50% of costs during the first year and thereafter biologic therapy steadily increased, accounting for more than 70% of costs for CD and 48% for UC by year 5. These findings align with our results. Furthermore, the mean yearly cost of biologic therapy

was higher in patients with CD (€1782) than in patients with UC (€286). Notably, costs incurred by comorbidities and unrelated to IBD were excluded from the analysis while our study included all costs in the analysis, which could explain differences observed between the two analyses.

An important strength of this study is that it provides real-world data on the patient characteristics and treatment patterns specifically in the Italian healthcare setting. In contrast to randomised controlled trials that provide results limited to the experimental conditions, real-world studies offer evidence on daily clinical practice.

Nevertheless, retrospective analyses based on administrative claims data provide limited or no clinical information on comorbidities, disease severity/status and other confounders that may have influenced results. The study did not capture data on the efficacy and tolerability profile of treatments prescribed. The selection of a defined study period, the historical data availability among LHUs databases and the proxy used for patient identification (hospitalisation or exemption code) could have influenced patient selection by including older patients into the analysis, not necessarily at the first disease onset and excluding outpatients who have not received an exemption code specific for IBD, thus limiting the identification of potential candidates. Estimates for the incidence of UC and CD for certain years were probably overestimated as a result of the update procedures for exemption databases included in the present analysis. In addition, the study was not designed to assess the cause and effect of prescribing decisions. For example, the reasons for dose escalation or de-escalation were not captured in the databases. In the stratification analyses, some of the subgroups had a small sample size. Although results may be representative of the overall population in Italy, there may be a need for further validation of results that include patient data from additional LHUs.

CONCLUSION

This study provides real-world data on the epidemiology (proxy of prevalence and incidence), patient characteristics, treatment patterns, healthcare resource use and costs for patients with UC and CD in Italy. Results show that, in recent years, most patients received IBD-related treatments, with a low proportion of patients receiving biologic treatments. This analysis may help to optimise therapy for patients with UC and CD and provide relevant clinical practice data to inform decision-makers.

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Data Availability. All data used for the current study are available upon reasonable request to CliCon Societa' Benefit S.r.l., which is the body entitled to data treatment and analysis by Local Health Units.

Declarations

Conflict of Interest. Melania Dovizio, Valentina Perrone, Chiara Veronesi and Luca Degli Esposti report no conflict of interest in this work. CliCon S.r.l. Società Benefit is an independent company. The agreement signed by CliCon S.r.l. Società Benefit and Eli Lilly and Company did not create any entityship, joint venture or any similar relationship between parties. Neither CliCon S.r.l. Società Benefit nor any of their representatives are employees of Eli Lilly and Company for any purpose. Susanne Hartz, Carlotta Buzzoni, Isabel Redondo and Marijana Nedeljkovic Protic are full-time employees and stock-holders of Eli Lilly and Company. Alessandro Armuzzi has received consulting fees from: AbbVie, Allergan, Amgen, Arena, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celltrion, Eli Lilly, Ferring, Galapagos, Gilead, Janssen, LionHealth, MSD, Mylan, Nestlè, Pfizer, Protagonist Therapeutics, Roche, Samsung Bioepis, Sandoz, Takeda; speaker's fees from: AbbVie, Amgen, Arena, Biogen, Bristol-Myers Squibb, Eli Lilly, Ferring, Galapagos, Gilead, Janssen, MSD, Novartis, Pfizer, Roche, Samsung Bioepis, Sandoz, Takeda, Tigenix; and research support from: MSD, Takeda, Pfizer, Biogen. Carlotta Buzzoni and Domenico Birra have changed affiliation during the completion of the manus their new affiliations are as follows: Carlotta Buzzoni, Epidemiology Unit, Agency for Health Protection (ATS) of Milan, C.so Italia 52, Milano 20122, Italy. Domenico Birra, Internal Medicine Unit – Asl Napoli 1 Centro – ODM Hospital, Naples, Italy.

Ethical Approval. The retrospective analysis of administrative databases involved secondary data extraction, and local ethics committees of each of the participating LHUs approved the study as per Agenzia Italiana del Farmaco (AIFA) guidelines and Italian law. Details of the local ethics committee, including name, protocol code and date of protocol approval are as follows: "Comitato etico interprovinciale Area I", Protocol 68/CE/20, approval date 3/12/2020; "Comitato Indipendente di Etica Medica", Protocol 48148, approval date 28/05/2021; "Comitato etico interprovinciale Area I", Protocol 10/CE/22, approval date 31/01/2022; "Comitato Etico Lazio 2", Protocol 0031401/2022, approval date 09/02/2022; "Comitato Indipendente di Etica Medica", Protocol 48144, approval date 28/05/2021; "Comitato Etico per la Sperimentazione Clinica della provincia di Venezia e IRCCS S. Camillo", Protocol 1405/AULSS 3 Mestre, approval date 26/10/2021; "Comitato Etico Regionale dell'Umbria", Protocol 19414/20/ON, approval date 27/10/2021; "Comitato Etico Interaziendale A.O. SS. Antonio e Biagio e Cesare Arrigo – Alessandria", Protocol AslVC.FarmT.21.02, approval date 16/12/2021. The study was conducted in compliance with ethical principles based on the Declaration of Helsinki and consistent with Good Pharmacoepidemiology Practices and applicable laws and regulations of Italy. All patient data collected were anonymised to ensure confidentiality and privacy. The anonymous univocal numeric code ensured total compliance with the European General Data Protection Regulation (GDPR) (2016/679). The results are exclusively in aggregated form and not attributable to a single institution, department, doctor, individual or individual prescribing behaviours. On the basis of the Data Privacy Guarantor Authority (General Authorisation for personal data treatment for scientific research purposes – n.9/2014), informed consent was not required, as its collection would be impossible for organisational reasons.

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