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Alimentary Tract

A retrospective analysis of treatment patterns, drug discontinuation and healthcare costs in Crohn's disease patients treated with biologics

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ABSTRACT

Background/aims: This real-world analysis evaluated the persistence and direct healthcare costs of Crohn's Disease (CD) patients treated with biologics in Italy.
Methods: A retrospective analysis on administrative databases of Italian healthcare entities, covering 10.4 million residents, was performed. Adult CD patients under biologics between 2015 and 2020 were included and attributed to first/second treatment line based on absence/presence of biologic prescriptions 5-years before index-date (first biologic prescription).
Results: Of 16,374 CD patients identified, 1,398 (8.5%) were biologic-treated: 1,256 (89.8%) in first line and 135 (9.7%) in second line. Kaplan-Meier curves estimated a higher persistence for ustekinumab-treated patients followed by vedolizumab, infliximab and adalimumab, in both lines. Considering baseline variables and adalimumab as reference, infliximab in first line (HR: 0.537) and ustekinumab in first (HR: 0.057) and second line (HR: 0.213) were associated with significantly reduced risk of drug-discontinuation. First line total/average healthcare direct-costs were €13,637, €11,201, €17,104 and €18,340 in patients persistent on adalimumab, infliximab, ustekinumab and vedolizumab, respectively.
Conclusions: This real-world analysis showed differences in persistence over 12-months between biologic treatments, being higher in ustekinumab-treated group, followed by vedolizumab, infliximab and adalimumab. Patients' management was associated with comparable direct healthcare costs among treatment lines, mainly driven by drug-related expenses.

1. Introduction

Inflammatory bowel disease (IBD) include Crohn's disease (CD) and ulcerative colitis (UC), two complex multifactorial immune-mediated disorders characterized by chronic relapsing inflammation of gastrointestinal tract [1]. CD targets various parts of digestive system, with periods of remission and relapse [2], and a progressively increasing recurrence risk, up to 90% at 10 years post-diagnosis [3,4]. CD patients can experience numerous comorbidities, including extra-intestinal manifestations. The debilitating nature of the disease profoundly impacts quality of life, at physical, psychological, and social levels [5].

IBD epidemiology with the related economic burden is highly variable worldwide. It has been reported that about 2.5–3 million people in Europe are affected by IBD, resulting in a direct healthcare cost of 4.6–5.6 bn Euros/year [6]. Epidemiological analyses of IBD in central Italy using administrative data sources estimated a prevalence of 177 and 144 (per 100,000) in males and females, re-

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spectively, for UC and 91 and 81 (per 100,000) for CD [7]. More recent Italian data found a prevalence every 100,000 inhabitants of 258.7 for UC and 135 for CD [8].

Currently, no drug therapy for CD patients is curative, and the therapeutic goals are to halt or reduce inflammatory burden, to induce a clinical and endoscopic remission to be maintained over an extended period [9]. Hence, achieving long-term remission represents an important clinical need, for which several treatments are currently used, starting from conventional therapies (aminosalicylates, corticosteroids and immunomodulators, including thiopurines and methotrexate), followed by biological therapies, namely monoclonal antibodies against tumor necrosis factor-α (anti-TNFα), like adalimumab, infliximab, certolizumab pegol (not approved by EMA), or integrins (vedolizumab) or interleukins 12/23 (ustekinumab) [6]. The medical management of CD has rapidly evolved and benefited from the growing availability of different pharmacological options [10]. The conventional therapeutic algorithm is based on a "step-up" strategy which requires the failure of corticosteroids and thiopurines before considering biologics. However, as the data regarding biological therapy accumulate, there is increasing evidence suggesting their early initiation in moderate-to-severe disease [11].

Based on 2020 European Crohn's and Colitis Organization (ECCO) Guidelines, to induce remission in patients with moderate-to-severe CD, anti-TNFα are recommended for non-responders to conventional therapy, while IL12/23 and integrin inhibitors should be used in case of inadequate response to conventional therapy and/or to anti-TNFα therapy [12]. In Italy, biologics are reimbursed by the National Health System (NHS) for CD patients unresponsive to conventional therapy. Besides anti-TNFα, the treatment with IL12/23 inhibitors and integrin inhibitors is reimbursed for patients with inadequate response to conventional therapy and/or to anti-TNFα or who are unsuitable to receive anti-TNFα as first biologic treatment [13].

As CD is a chronic disease which requires long-term treatment to sustain remission and clinical response, as well as to control symptoms and prevent disease progression, treatment persistence and drug discontinuation rates represent important variables to be considered. In Italy, poor data in the real-world setting are available on these important features due to a lack of studies on regional or national healthcare databases. Thus, the present analysis aimed to investigate the treatment patterns, the drug utilization in terms of therapy discontinuation in moderate-to-severe CD patients who received biological medications between 2015 and 2020 by using real-world data in Italy. Moreover, the economic burden was also evaluated by estimating the healthcare costs covered by the Italian NHS.

2. Methods

2.1. Data source

This is a retrospective observational study on data from the administrative databases of a pool of geographically distributed Italian healthcare departments (belonging to Puglia, Calabria, Campania, Lazio, Abruzzo, Umbria, Veneto, Piemonte, Liguria regions), covering approximately 10.4 million health-assisted individuals by the Italian NHS. Data were extracted from demographic database, pharmaceuticals database, hospitalization database, outpatient specialist services database, and payment exemption database (Supplementary Material) and the linkage among all databases allowed to define the patient' clinical and chronological profile. For the current study, Italian Entities database were selected by their geographical distribution, data completeness, and high-quality linked datasets. An anonymous univocal numeric code was assigned to each subject to guarantee patients' privacy, in full conformity with the European General Data Protection Regulation (GDPR) (2016/679). The patient code in each database permitted the electronic linkage between databases. The results were produced as aggregated summaries and never attributable to a single institution, department, doctor, individual, or individual prescribing behaviours. The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committees of the healthcare departments involved.

2.2. Study design and population

Between January 2015 and December 2020 (inclusion period), among the study population, all adult CD patients with a moderate-severe disease were identified by (a) presence of at least one hospitalization discharge diagnosis for CD (ICD-9-CM code 555) or disease exemption code 009.555 and (b) prescription with biological medications indicated for CD [infliximab (ATC code L04AB02), adalimumab (ATC code L04AB04), vedolizumab (ATC code L04AA33), ustekinumab (ATC code L04AC05)]. The index-date was that of the first biologic prescription. All patients were characterized throughout the 12-months before index-date and followed-up for all available period after index-date. Patients with a diagnosis of UC (identified by the ICD-9-CM code 556 or exemption code 009 or 009.556), and patients who moved out from the region (relocation) were excluded.

2.3. Baseline demographic and clinical patients' characteristics

At index-date, patients' demographics were recorded, namely age, and gender (proportion of males). During the characterization period, comorbidity profile was assessed through the Charlson comorbidity index (CCI) [14]. Previous diagnoses of psoriasis (PSO), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) were also searched during the characterization period: PSO was identified by the presence of at least one prescription of topical antipsoriatic drugs (ATC code: D05A), or exemption code 045.696.1, or at least one hospital discharge (at any diagnosis level) with the ICD-9-CM code 696.1; PsA by the presence of at least one hospital discharge ICD-9-CM code 696.0 and/or an exemption code 045.696.0; AS by the presence of at least one hospital discharge ICD-9-CM code 720.0 and/or an exemption code 054.720.0.

2.4. Biologic treatment pattern and definition of lines of therapy

Treatment patterns and therapy lines were analysed at index-date and during the full available follow-up. At index-date, treatment patterns were evaluated by the number of treatment lines: patients in first line were identified as bio-naïve (without prescriptions of biologics during the last 5 years before index-date). Patients in second, third and fourth lines corresponded to bio-experienced patients, or patients with at least one biologic prescription, different from that identified at index-date or before. During follow-up, patients who remained with the same biological agent of index-date were defined as first line, while those who changed once the biological agent of index-date and started another biological agent were referred as in second line treatment. For the analysis of drug persistence and healthcare costs, patients under first or second line treatment were followed until they remained on treatment with the index-medication or until the end of study period (including death), whichever came first.

2.5. Drug discontinuation free event survival

Drug discontinuation was defined when patients on treatment with a biologic drug did not receive a subsequent prescription within the grace period, calculated from the date of the last prescription received, or death for any cause. This method allows to estimate the persistence to treatment considering a degree of tolerance in the gap between prescriptions, which for patients in chronic treatment may not be an indication of complete treatment suspension and therefore of non-persistence [15,16].

For the analysis, the grace period corresponded to the 2-fold of the length of the prescribing interval during the maintenance phase according to summaries product characteristics (SmPC) (i.e. for ustekinumab, 12-week maintenance according to SmPC corresponds to a 24-week grace period). Survival curves were built using Kaplan-Meier method, censored for patients who dropped out from the study for any reason, e.g. death or lost at follow-up. The analysis was truncated at 12 months so that all patients had exactly 1-year of follow-up.

2.6. Average direct healthcare costs covered by the NHS

During follow-up, the total average direct costs covered by the Italian NHS, relating to biologics and other drug prescriptions (reimbursed by the Italian NHS, and using the Italian NHS purchase price, both for originators or biosimilars), hospitalizations (determined by using the DRGs tariffs), and specialist services (i.e. specialist visits and diagnostic tests, according to Regional tariffs) were assessed. Data were reported as the mean total healthcare cost per patient. Outliers, defined as values exceeding the mean value three times the standard deviation (SD), were excluded from cost analysis. Healthcare cost data referring to the first year of follow-up were described, while those of the subsequent years could not be reported due to low sample size in some subgroups.

2.7. Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD), categorical variables as frequencies and percentages. For statistical comparison among Kaplan Meier curves, a log-rank test was applied and $p<0.05$ was considered statistically significant. Multivariate regression model was applied to evaluate the association between the use of different biological drugs and treatment persistence, considering the demographic and baseline clinical variables (treatments, age, gender, CCI, inclusion year). Among the treatments included in this regression model, adalimumab was considered as reference since adalimumab-treated group had the largest sample size. The hazard ratios (HR) and 95% confidence intervals (CI) were reported. In addition, a generalized linear model (GLM) was developed to evaluate the correlation between the index-medication and healthcare costs among patients, checking for confounding factors such as age, gender, CCI, and the mean cost evaluated during the year before index-date. All analyses were performed using Stata SE version 17.0 (StataCorp, College Station, TX, USA). According to "Opinion 05/2014 on Anonymization Techniques" drafted by the "European Commission Article 29 Working Party", the analyses involving fewer than 3 patients were not disclosed, as they were potentially traceable to single individuals. Therefore, results referred to ≤ 3 patients were reported as NI (not issuable).

3. Results

Overall, during the inclusion period 16374 CD patients were identified and among them 1398 (8.5%) patients were included if they received at least one prescription of biological medications during the inclusion period; they were identified as patients with active moderate-severe disease. CD patients were stratified according to the type of biological drug prescribed at index-date: 58.4% were treated with adalimumab, 26.6% with infliximab, 9.3% with vedolizumab and 5.7% with ustekinumab. In the overall CD cohort, 55.4% patients were male, and the included population was aged 40.8 ± 15.3 years: in particular, 39.5 ± 14.4 and 39.4 ± 14.9 years for adalimumab- and infliximab-treated patients, respectively, and 48.7 ± 18.8 and 46.8 ± 15.3 years for vedolizumab and ustekinumab patients, respectively. The CCI averaged 0.5 ± 0.7 in the overall cohort, as well as in adalimumab-, vedolizumab-, and ustekinumab-treated patients, and 0.4 ± 0.7 among infliximab users. Concerning concomitant diseases, 8.3% had a previous diagnosis of PSO and/or PsA and 4.3% of AS (Table 1). As reported in Supplementary Table 1, the monthly dosages during the maintenance phase are reported in weeks and were comparable to the label recommendations.

During the 5-year follow-up period, 81.2% of CD patients (1256) remained in first line treatment with the index-biologicals: specifically, 61.5% of patients were in first line with adalimumab, 27.7% with infliximab, and 6.8% and 4.0% with vedolizumab and ustekinumab, respectively (Fig. 1A). Differently, 15.2% ($N = 135$) of overall included patients changed the index-drug, thus being classified as patients in second line or further lines during the follow-up. Specifically, 33% and 22% were in second line with adalimumab and infliximab, respectively, and 19.7% and 25.2%, were receiving vedolizumab and ustekinumab (Fig. 1B). Due to the low sample size, data of third line patients were not shown.

The characteristics of patients stratified by line of therapy are reported in Table 2. Patients in first and second line respectively were aged 40.6 ± 15.4 and 41.6 ± 14.7 years at inclusion, and 55.1% and 57.0% were males. The CCI averaged 0.4 ± 0.7 in first line and 0.6 ± 0.8 in second line-treated patients. Drug discontinuation was evaluated in first line and second line patients (Fig. 2) by Kaplan-Meier survival curves. Among patients in first line treatment followed-up to 12 months, a difference treatment persistence was found between subgroups ($p<0.001$) (Fig. 2A). The multivariate analysis was performed to predict the probability of treatment discontinuation by adjusting for baseline variables and showed that, with respect to adalimumab (reference), in first line treatment, infliximab (HR: 0.537, 95%CI: 0.412–0.701, $p<0.001$) and ustekinumab (HR: 0.057, 95%CI: 0.008–0.404, $p = 0.004$) were associated with a reduced probability to discontinue the treatment, while among vedolizumab-treated patients a not statistically significant trend was observed (HR: 0.740, 95%CI: 0.471–1.161, $p = 0.190$). Moreover, for patients in first line treatment, the inclusion year (from 2016 to 2020) significantly predicted the risk of discontinuation with respect to 2015 considered as reference (Supplementary Table 2).

A similar trend was observed using Kaplan Meier survival curves among patients on second line treatment (Fig. 2B), where the treatment of ustekinumab was associated with a lower probability of treatment discontinuation. This finding was confirmed by multivariate regression model showing that, with adalimumab as reference, second line treatment with ustekinumab resulted in a probability of discontinuation decreased by 79% (HR: 0.213, 95%CI: 0.105–0.432, $p<0.001$), while a not significant trend was found among infliximab (HR: 0.702, 95%CI: 0.444–1.109, $p = 0.129$) and vedolizumab-treated patients (HR: 0.687, 95%CI: 0.408–1.154, $p = 0.156$). In second line, the variable age was significantly associated with a lower probability of treatment discontinuation (HR: 0.980; 95%CI: 0.966–0.994, $p = 0.006$). In second line treated patients, the years of inclusion 2017, 2018 and 2019 were significantly correlated with a lowered risk of drug discontinuation (Supplementary Table 3).

The estimation of direct healthcare costs for the management of biologic-treated CD patients is reported in Table 3. Among patients in first line treatment, during one-year follow-up, the mean total direct annual cost per patient was equal to €13637, €11201, €17104 and €18340 in patients treated with adalimumab, infliximab, ustek-

Table 1
Baseline characteristics of overall CD patients and those stratified by the biological agent prescribed at the index-date.

	Overall CD patients $N = 1398$	Adalimumab $N = 816$ (58.4%)	Infliximab $N = 372$ (26.6%)	Ustekinumab $N = 80$ (5.7%)	Vedolizumab $N = 130$ (9.3%)
Age, years (mean, SD)	40.8 (15.3)	39.5 (14.4)	39.4 (14.9)	46.8 (15.3)	48.7 (18.8)
Age 18–29 years	406 (29.0)	246 (30.1)	127 (34.1)	8 (10.0)	25 (19.2)
Age 30–39 years	287 (20.5)	183 (22.4)	63 (16.9)	20 (25.0)	21 (16.2)
Age 40–49 years	292 (20.9)	169 (20.7)	77 (20.7)	20 (25.0)	26 (20.0)
Age 50–59 years	224 (16.0)	133 (16.3)	62 (16.7)	15 (18.8)	14 (10.8)
Age 60–69 years	131 (9.4)	68 (8.3)	37 (9.9)	9 (11.3)	17 (13.1)
Age 70+ years	58 (4.1)	17 (2.1)	6 (1.6)	8 (10.0)	27 (20.8)
Male gender (n,%)	775 (55.4)	431 (52.8)	222 (59.7)	36 (45.0)	86 (66.2)
CCI (mean, SD)	0.5 (0.7)	0.5 (0.7)	0.4 (0.7)	0.5 (0.7)	0.5 (0.7)
PSO/PsA (n,%)	115 (8.2)	75 (9.2)	23 (6.2)	11 (13.8)	6 (4.6)
AS (n,%)	60 (4.3)	<4	15 (4.0)	<4	40 (4.9)

Abbreviations: AS, ankylosing spondylitis; CCI, Charlson comorbidity index; CD, Crohn's disease; PSO, psoriasis; PsA, psoriatic arthritis.

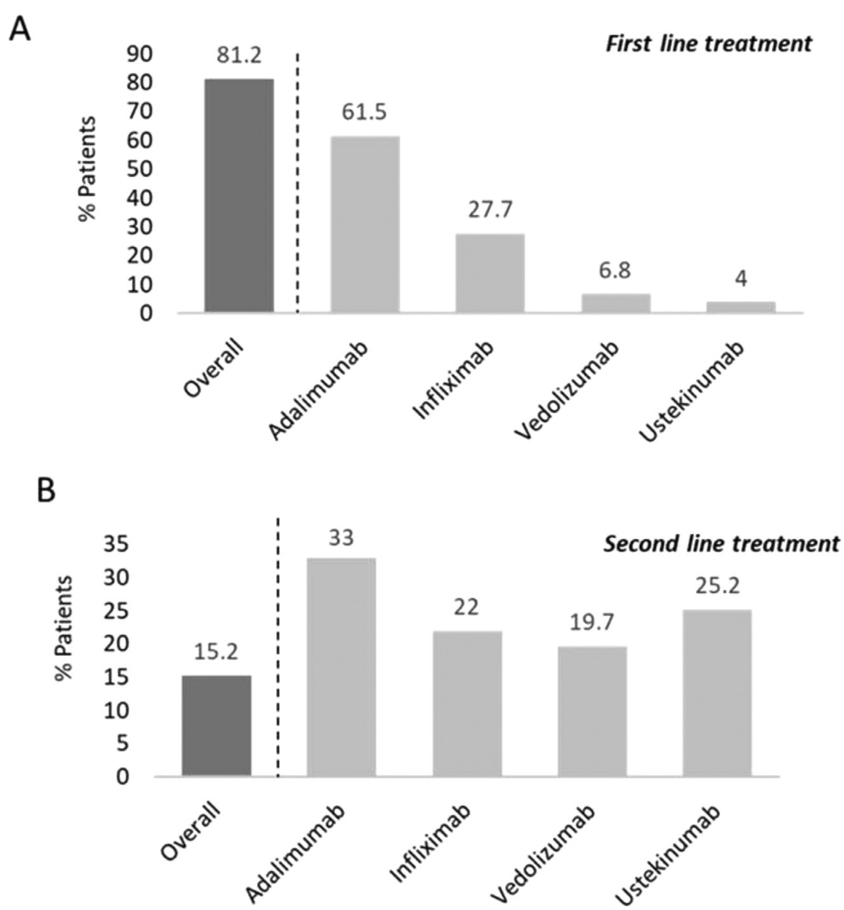

Fig. 1. Treatment pattern during the follow-up period in patients stratified by line of treatment.

Table 2
Baseline characteristics of CD patients stratified by line of treatment at index-date.

	First line	Second line
Patients, n	1256	135
Age, years (mean, SD)	40.6 (15.4)	41.6 (14.7)
Age 18–29 years	371 (29.5)	35 (25.9)
Age 30–39 years	256 (20.4)	29 (21.5)
Age 40–49 years	260 (20.7)	30 (22.2)
Age 50–59 years	202 (16.1)	21 (15.6)
Age 60–69 years	114 (9.1)	16 (11.9)
Age 70+ years	53 (4.2)	4 (3.0)
Male gender (n,%)	692 (55.1)	77 (57.0)
CCI (mean, SD)	0.4 (0.7)	0.6 (0.8)

Abbreviations: CCI, Charlson comorbidity index.

inumab and vedolizumab, respectively. The analysis of costs during one-year before treatment initiation estimated €3026 for adalimumab, €2641 for infliximab, €4380 for ustekinumab, and €4999 for vedolizumab-treated patients. Among patients in second line of treatment, during one-year after (and before) the treatment start, the average total cost/patients was €14644 (and €9462) in adalimumab, €12,199 (and €11,291) in infliximab, €17270 (and €7892) in ustekinumab, and €18175 (and €7933) in vedolizumab-treated patients The detailed description of healthcare costs for the management of CD patients in first and second line with biologics in the year before and after index-date divided by cost items (biologics, other drugs, hospitalization, specialist visits, and diagnostic tests) is reported in Supplementary Table 4. The GLM was performed to identify predictors of total mean costs: as reported in Table 4, respect to the reference molecule adalimumab, in both first and

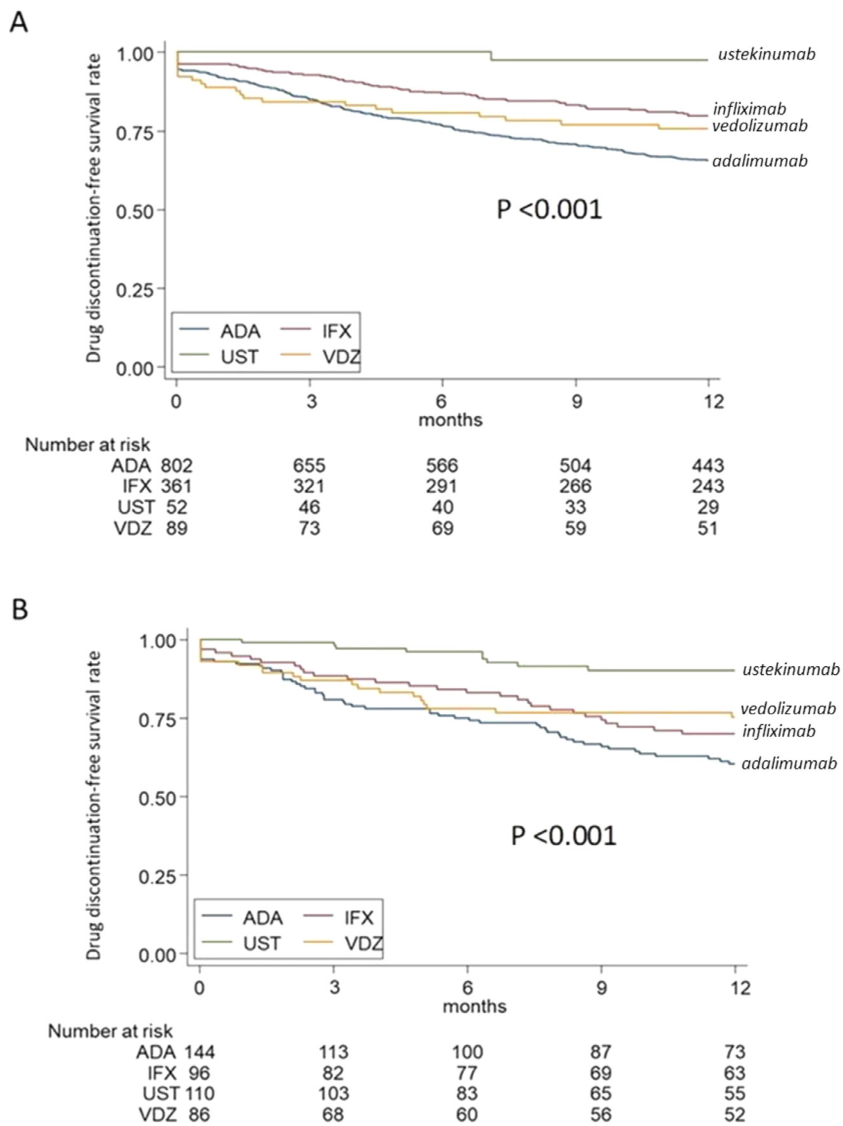

Fig. 2. Kaplan Meier curve of drug discontinuation around the grace period, of **(A)** first line and **(B)** second line treatment. Abbreviations: ADA, adalimumab; IFX, infliximab; UST, ustekinumab; VDZ, vedolizumab.

Table 3
Healthcare direct costs for the management of CD patients during one year before (pre) and after (post) index-date.

	Adalimumab		Infliximab		Ustekinumab		Vedolizumab	
	pre	post	pre	post	pre	post	pre	post
Patients in first line Total costs (€)	3026	13637	2641	11201	4380	17104	4999	18340
Patients in second line Total costs (€)	9462	14644	11,291	12199	7892	17270	7933	18175

First line: Adalimumab ($N = 516$); Infliximab ($N = 186$); Ustekinumab ($N = 23$); Vedolizumab ($N = 38$). *Second line*: Adalimumab ($N = 88$); Infliximab ($N = 63$); Ustekinumab ($N = 43$); Vedolizumab ($N = 33$).

second line setting, the treatment with infliximab resulted in significantly reduced total costs at one-year follow-up, while ustekinumab and vedolizumab were associated with increased costs. Moreover, older age was also a significant predictor of increased healthcare expenses either in first line ($p = 0.010$) or in second ($p = 0.014$) treatment lines.

4. Discussion

This real-world investigation on patients with moderate-severe CD under biological therapy focused on treatment patterns, drug utilization, and healthcare resource consumptions among the Italian population.

In the present analysis, 1398 CD patients under biological treatment between 2015 and 2020 were identified, which represent almost 8.5% of all CD patients intercepted in the same period, in line with previous Italian data suggesting an underutilization of biologics in potentially eligible CD patients [17]. Among them, at the study inclusion, almost 89% were in first line treatment with an anti-TNFα drug (adalimumab and infliximab), 7% with vedolizumab and 4% with ustekinumab. In second line, almost half of the patients were under anti-TNFα therapy, while 20%

Table 4
Generalized linear model (GLM) for predictors of mean total direct cost evaluated during one-year follow-up. Significant P values are in bold.

Patients in first line	HR	95% CI		p value
Adalimumab	REF.			
Infliximab	−2266.2	−3151.5	−1380.8	**<0.001**
Ustekinumab	2833.8	−307.1	5974.8	0.077
Vedolizumab	3894.3	1257.4	6531.1	**0.004**
Cost 1 yr pre, thousands	143.7	32.0	255.4	**0.012**
Age at inclusion	38.7	9.1	68.2	**0.010**
Male gender	−186.6	−1022.5	649.3	0.662
Charlson comorbidity index	250.9	−414.8	916.6	0.460
Constant	11,658.0	10,352.1	12,963.9	<0.001
Patients in second line				
Adalimumab	REF.			
Infliximab	−2310.2	−3986.7	−633.6	**0.007**
Ustekinumab	4458.7	1962.3	6955.1	**<0.001**
Vedolizumab	4053.4	1232.0	6874.8	**0.005**
Cost 1 yr pre, thousands	339.4	204.6	474.2	**<0.001**
Age at inclusion	68.1	13.5	122.8	**0.014**
Male gender	292.4	−1259.1	1843.8	0.712
Charlson comorbidity index	1286.9	−349.9	2923.6	0.123
Constant	7675.6	4617.0	10,734.3	<0.001

and 25% were prescribed vedolizumab and ustekinumab, respectively. This treatment profile reflects both guidelines' statements and drug reimbursement criteria by the Italian Medicines Agency (AIFA), which provides the reimbursement of vedolizumab and ustekinumab in patients with inadequate response or intolerant to conventional therapies and/or to anti-TNFα agents [6,17]. Besides, the availability of biosimilars for infliximab and adalimumab as potentially cost-effective alternatives, and the fact that vedolizumab and ustekinumab represent the most recently approved medications, could impact the treatment management of CD patients [18].

Persistence was defined as the duration of time from initiation to discontinuation of therapy (based on grace period gap) and evaluated using Kaplan-Meier survival curves. In patients on first line therapy, at one-year follow-up a higher probability for treatment maintenance in ustekinumab-treated patients was found, followed by vedolizumab, infliximab and adalimumab. A similar scenario was observed in second line-treated patients. This trend remained similar, also following patients up to 2 years (not shown). Despite very limited evidence on persistence of biological treatments is available among CD Italian patients, these data are in line with previous population-based studies in European and non-European clinical setting [19–21].

The analysis of direct healthcare costs for the management of biologic-treated CD patients showed that in the study population, the average overall annual cost was 13006€; in patients stratified by drug, the total annual cost ranged from 11263€ (infliximab) to 17209€ (vedolizumab), with the biologic-related expenditures based on ex-factory price being the weightiest cost item, accounting for more than 80% of the total direct costs, and with the other medical cost items being less than 20% of the total expenditure. These data could be explained by the fact that the economic analysis was carried out in persistently treated patients with the index-biologic medication. It has been reported that in IBD patients treated with biologics, both the adoption of an optimal treatment regimen [22], as well as the high persistence [23,24] and adherence rates [25] could positively impact the healthcare costs, mainly by reducing inpatient expenditures [23–25].

Moreover, the analysis of variables potentially predicting the costs at the first year of follow-up highlighted that the expenditures sustained during the year before inclusion significantly affected the economic burden of CD management. These results seem to suggest that patients' baseline demographic and clinical conditions could impact sustainability of CD patients during their treatment with biologics. Our cost analysis is largely consistent with real-world data from Germany [26], indicating that biologic therapy itself, together with inpatient treatments, represent the main cost drivers in the management of patients with IBD treated with biologics. However, compared to the present analysis, the authors also investigated the prescribed dosage of biological drugs during maintenance phase and found that most patients received a higher dosage than that specified in label recommendations across all the observed biologic agents: this aspect might represent a significant contributor to the elevated impact of biological drug expenses in the German study [26].

The results of the present analyses should be interpreted in light of some limitations related to its retrospective observational nature and the use of anonymized data derived from administrative databases. Region/LHUs administrative databases have progressively improved the quality of the collected data. Nevertheless, some data may be missing and to overcome such problem, if a necessary information was unavailable for a given patient, that patient was excluded from the analysis. In addition, there was lacking or partial clinical information on comorbidities, disease severity, and other potential confounders that could have influenced the present results. Since comorbidity profile was assessed using proxy of diagnosis on data extrapolated from administrative flows before inclusion, there might be an incomplete information about patients clinical status. Multivariate models were constructed on available and captured variables; thus, other covariates (not retrieved in the current analysis) could have impacted treatment persistence and healthcare costs. Data on pharmacological treatments were collected from medical prescription and dispensing information; the evaluation of persistence by grace period could represent a study limitation as some drugs' dosage schedules may have influenced the analysis by contributing to the observed persistence rates [27]. The reasons behind treatment discontinuation as well as the impact of treatment regimens, such as the combo treatment with immunomodulators which it has been reported to impact biologic treatment discontinuation in IBD patients [28], were not captured in the current analysis. Patients were identified bio-naïve or bio-experienced based on the 5-year period before index-date; this criterion could have underestimated bio-experienced patients. Finally, some subgroups had a small sample size and with some of them too small to be analysed.

In conclusion, this real-world data analysis reported the evaluation of treatment pattern, drug utilization, and disease economic burden in CD patients treated with biologics in Italy between 2015 and 2020. The results showed that the treatment pattern among the different biologics was in line with the current recommendation and the Italian reimbursement criteria. Drug discontinuation rate was variable across the biological drugs analysed, as ustekinumab appeared to be associated with a lower probability of treatment discontinuation, followed by vedolizumab, infliximab, and adalimumab. The analysis of healthcare costs in persistently bio-treated patients revealed that the highest expenditures in the management of CD patients were primarily driven by expenditures for biologics. Moreover, the economic burden of a patient was associated to the period prior to biologic treatment start and suggests an impact on direct healthcare costs during biologic therapy.

Availability of data and materials

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

Conflict of Interest

Janssen-Cilag SpA purchased the study report that is the basis for this manuscript. This manuscript was developed with Janssen-

Cilag SpA and CliCon S.r.l. Società Benefit. The views expressed here are those of the authors and not necessarily those of the supporters. The agreement signed by CliCon S.r.l. and Janssen-Cilag SpA does not create any entity, joint venture or any similar relationship between parties. CliCon S.r.l. is an independent company. Neither CliCon S.r.l. nor any of their representatives are employees of Janssen-Cilag SpA for any purpose.

Andrea Franchi, Ottavio Secchi and Andrea Serra are employees of Janssen-Cilag SpA.

Marco Daperno served as member of boards, lecturer and/or received grants for participation to congresses from Abbvie, Takeda, Jannsen, Pfizer, Celltrion, Galapagos, SOFAR, Chiesi, Zambon, Ferring; he acts as consultant for Bioclinica-Clario.

Edoardo Vincenzo Savarino has served as speaker for Abbvie, AGPharma, Alfasigma, Dr Falk, EG Stada Group, Fresenius Kabi, Grifols, Janssen, Innovamedica, Malesci, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Unifarco; has served as consultant for Alfasigma, Amgen, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Dr. Falk, Fresenius Kabi, Janssen, Merck & Co, Reckitt Benckiser, Regeneron, Sanofi, Shire, SILA, Sofar, Synformulas GmbH, Takeda, Unifarco; he received research support from Pfizer, Reckitt Benckiser, SILA, Sofar, Unifarco.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.04.010.

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