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Alimentary Tract

Estimation of patients affected by inflammatory bowel disease potentially eligible for biological treatment in a real-world setting ☆

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ABSTRACT

Background/aims: This analysis estimated the number of inflammatory bowel disease (IBD) patients presenting criteria of eligibility for biological therapies in an Italian real-world setting.
Methods: An observational analysis was performed on administrative databases of a sample of Local Health Units, covering 11.3% of the national population. Adult IBD patients (CD or UC) from 2010 to the end of data availability were included. Eligibility criteria for biologics were the following: Criterion A, steroid-refractory active disease; Criterion B, steroid-dependent patients; Criterion C, intolerance or contraindication to conventional therapies; Criterion D, severe relapsing disease; Criterion E (CD only), highly active CD disease and poor prognosis.
Results: Of 26,781 IBD patient identified, 18,264 (68.2%) were treated: 3,125 (11.7%) with biologics and 15,139 (56.5%) non-biotreated. Among non-biotreated, 7,651 (28.6%) met at least one eligibility criterion for biologics, with criterion B (steroid-dependence) and criterion D (relapse) as the most represented (58–27% and 56–76%, respectively). Data reportioned to the Italian population estimated 67,635 patients as potentially eligible for biologics.
Conclusions: This real-world analysis showed a trend towards undertreatment with biologics in IBD patients with 28.6% being potentially eligible, suggesting that an unmet medical need still exists among the Italian general clinical practice for IBD management.
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1. Introduction

Inflammatory bowel diseases (IBD) are chronic and life-long diseases characterized by inflammation in the gastrointestinal tract (GI) [1]. IBD includes ulcerative colitis (UC) and Crohn's disease (CD), which are discernible by their location and nature of inflammation. UC and CD are two different diseases, and "IBD" represents an umbrella term for the two chronic conditions. UC affects the colonic mucosa, while CD can affect the entire thickness of any part of the GI tract [2]. Both UC and CD are characterized by relapsing chronic intestinal inflammation and represent debilitating conditions without a definitive cure. As of 2017, 6.8 million IBD cases were reported globally, increasing age-standardized prevalence rates from 79.5 per 100,000 in 1990 to 84.3 per 100,000 population in 2017 [3]. In Europe, the prevalence for CD and UC ranges from 6.76 to 135.6 per 100,000 and 21.10–198 per 100,000, respectively [4]. Across 1990–2016, the prevalence for CD among the Italian population was estimated as 6.76–25/100,000, and UC as 21.10–44.30/100,000 [4]. These diseases mainly affect young-adult population ranging 15–40 years [5]. In particular, UC shows the highest incidence between 20 and 40 years, while Crohn's disease in the age range 15–35 years [5]. Similarly, to most chronic diseases, IBD results in a significant reduction in the quality of life [6], while

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representing a high consumption of healthcare resources, in terms of recurrence to medications and hospitalizations [7,8].

IBD therapeutic options comprise conventional medications (including aminosalicylates, corticosteroids, and immunomodulators), and biologics, i.e. monoclonal antibodies against tumor necrosis factor-α [anti-TNFα, namely infliximab, adalimumab, golimumab (approved by EMA only for UC) and certolizumab pegol (not approved by EMA for IBD treatment)] and against integrins (vedolizumab) or interleukins (ustekinumab) [9–11]. In the last few years also small molecules (Janus kinase inhibitors or Sphingosine phosphate 1 receptor modulators) have been licensed for the treatment of UC. In fact, the recent Italian guidelines stated by the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) recommend using any of the biologics currently available or tofacitinib to induce remission of moderate to severe UC that is refractory to conventional therapy in adults who are naïve to biologics [9–11]. To reduce the risk of complications and improve patient quality of life, the IBD management has a primary goal the induction and maintenance of symptoms and endoscopic remission [12,13], and to reduce the need for long-term corticosteroids treatment, which are generally used in the first instance for both moderate-to-severe UC and CD [14]. The advent of biologics, firstly introduced in late 90 s, has transformed the management of IBD with enhanced early and deep responses to treatment, allowing the reduction of hospitalizations, and the need for surgery [15]. Despite their availability, it has been claimed that among UC patients, surgery is still required for 20%−30% of patients during their life [15,16], and only 13% of patients use biologic agent [17]. This underuse of biologics among IBD patients could be possibly related to the lack of real-world evidence in support of early biologic treatment. In this setting, evidence from the routine clinical practice could suggest opportunities for improving the therapeutic management of IBD patients.

Thus, the aim of the present analysis was to estimate the number of IBD patients with CD or UC diagnosis, their treatment pattern and to identify those potentially eligible to biological therapies, in a large Italian real-world setting.

2. Material and methods

2.1. Data source

In this retrospective observational study, data were collected from Italian Healthcare Departments' administrative databases, for a sample representing around 11.3% of the entire national population. Data were then re-proportioned to the Italian population.

The following databases were used: i) demographic database, which consists of all patient demographic data, such as gender, age and death; ii) pharmaceuticals database, that supplies information on medicinal products reimbursed by the INHS as the Anatomical Therapeutic Chemical (ATC) code, number of packages, number of units per package, unit cost per package, and prescription date; iii) hospitalization database, which encloses all hospitalizations data for patients in analysis, such as the discharge diagnosis codes classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), Diagnosis Related Group (DRG) and DRG related charge (provided by the Italian Health System); iv) outpatient specialist services database, which incorporates all information about visits and diagnostic tests for patients under analysis (date and type of prescription, description activity and laboratory test or specialist visit charge); v) payment exemption database, which contains data of the exemption codes that allow to avoid the contribution charge for services/treatments when specific diseases are diagnosed.

An anonymous univocal numeric code was assigned to each study 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 among all databases. All the results coming out from the analyses were produced as aggregated summaries, which cannot assign, either directly or indirectly, to individual patients. 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. Identification of study population and definition of treated and untreated patients

Payments with IBD (CD or UC) diagnosed from 2010 to the end of data availability (September 2019) were included. Diagnoses were identified by the presence of at least one hospitalization with a primary or secondary diagnosis for UC or CD with ICD-9-CM codes 556 or 556, respectively, and/or an active exemption code 009.556 (for UC) or 009.555 (for CD). The presence of the disease exemption code was searched from 2000 to the end of the study period. Patients were identified as treated or untreated based on the presence, or not, of at least one prescription of the following medications indicated for IBD, during the most recent years (September 2018-September 2019, drug utilization period); in particular were defined bio-treated if presented at least one prescription of biologicals [including adalimumab (ATC code L04AB04), golimumab (ATC code L04AB06), infliximab (ATC code L04AB02), certolizumab (ATC code L04AB05) ustekinumab (ATC code L04AC05), vedolizumab (ATC code L04AA33)]; non-bio-treated if were prescribed with conventional medications such as intestinal anti-inflammatory agents [including corticosteroids acting locally (ATC code A07EA),5-aminosalicylates and similar agents (ATC code A07EC)] or other drugs [methotrexate (ATC code L01BA01), cyclosporine (ATC code L04AD01), azathioprine (ATC code L04AX01), mercaptopurine (ATC code L01BB02), tofacitinib (ATC code L04AA29), tacrolimus (ATC code L04AD02), and systemic corticosteroids (ATC code H02, excluding beclomethasone nasal spray)]. Patients were defined as never treated if they did not present any IBD-related drug prescription during all available periods. The index date was set as the last available date in the database, and the evaluation of all variables was assessed by considering the period before the index date. The follow-up was all the period of data availability after the index date. Patients who died during follow-up were excluded from the analysis.

2.3. Definition of criteria of potential eligibility for biologicals and characterization of untreated patients

In Table 1, the criteria applied to identify IBD patients potentially eligible for biologicals have been reported. For patients untreated or non-bio-treated, five criteria have been identified and applied by considering all available period: criterion A for the identification of patients with steroid-refractory active disease defined in spite of an adequate dose and duration of prednisone (0.75–1 mg/kg/day for at least 2 weeks) and identified by using as a proxy the evaluation of patients who switched to intestinal anti-inflammatory agents or other drugs (conventional drugs, no biologics) after 2 weeks therapy with prednisone or prednisolone up to 0.75–1 mg/kg/day [11]; criterion B for the identification of steroid-dependent patients [11] [by using as a proxy the evaluation of systemic corticosteroids or budesonide for a period $\geq$3 months without clinical relapse or relapse within 3 months after stopping corticosteroids (see the criteria D for the definition of clinical relapse); criterion C for the identification of patients with intolerance or contraindication to conventional therapies [18] [by using as a proxy the evaluation of effects associated with steroid treatment, i.e. early effects, those associated with prolonged use (usually >12

Table 1
Criteria applied to identify IBD patients potentially eligible for biological therapies.

Criteria	Proxy
A. Patients with steroid-refractory active disease can be defined as patients who have active disease despite prednisone up to 0.75 mg/kg/day for 2 weeks [11]	• **Switch to another drug different from biological agents** (intestinal anti-inflammatory agents or other drugs) **after therapy with prednisone** (ATC A07EA03, H02AB07) **or prednisolone** (ATC A07EA01, H02AB06) **up to 0.75 mg/kg/day for a period of 2 weeks**
B. Patients steroid-dependent can be defined as patients with inability to stop systemic steroids within 3 months or budesonide, without clinical relapse or relapse within 3 months after steroid weaning [11]	• **Treatment with systemic corticosteroids** (ATC H02) **or budesonide** (ATC A07EA06) **for at least 3 months and without clinical relapse** (defined as criterion D), **OR** • **Relapse** (defined as criterion D) **within 3 months after stopping systemic corticosteroids** (ATC H02)
C. Patients intolerance or contraindication to conventional therapies can be defined as presence of adverse effects of steroids [18]	• **Early effects**: cosmetic effects [acne (ICD9 706.1), moon face (ICD9 759.89), edema (ICD9 782.3), skin striae (ICD9 701.3)] sleep and mood disturbance (ICD9 780.50), dyspepsia (ICD9 536.8) or glucose intolerance (ICD9 790.2), **OR** • **Effects associated with prolonged use** [usually > 12 weeks]: posterior subcapsular cataracts (ICD9 366), osteoporosis (ICD9 733.0), glaucoma (ICD9 365.4), osteonecrosis of the femoral head (ICD9 733.4), myopathy (ICD9 359.9), infection (ATC J01), new onset diabetes mellitus (ATC A10) and hypertension (ATC C02, C03, C07, C08, C09), **OR** • **Effects during withdrawal include** acute adrenal insufficiency (ICD9 255.4), a syndrome of pseudo-rheumatism [with myalgia (ICD9 729.1), malaise (ICD9 780.79) and arthralgia (ICD9 719.4)] or raised intracranial pressure (ICD9 348.2)
D. Patients with severe disease that have relapse could be defined by use of high-dose corticosteroids or dose increase, gastrointestinal-related hospitalization [19,20]	• **Dose increase** (defined as presence of at least 1 prescription above initial dose during the 3 months period), **OR** • **Gastrointestinal-related hospitalization** (CD/UC main diagnosis)
Additional criteria for CD	
E. CD patients with highly active disease and poor prognosis can be defined as patients with extensive disease, needing initial treatment with steroids or with perianal disease at diagnosis [11,21]	• **Starting treatment with systemic corticosteroids** (ATC H02), **OR perianal disease** (ICD9 555.9, 566) at CD diagnosis

weeks) and those manifesting during drug withdrawal]; criterion D for the identification of disease relapse [19,20] identified by increased corticosteroid dose (at least one prescription above initial dose within 3 months) or hospitalization discharge diagnosis with CD or UC as primary diagnosis; criterion E (only for CD patients) for the identification of CD patients with highly active disease and poor prognosis [18,21] [by using as a proxy the start with systemic corticosteroid treatment or with concomitant perianal disease at CD diagnosis]. The criteria applied were developed based on the guidelines and the available literature during the analysis and were refined and validated by a pool of clinicians specialized in gastroenterology.

In untreated patients, age and gender have been identified and reported at the inclusion. During all available period before the index date, previous IBD-related hospitalization, and previous gastrointestinal visits (by the procedural code 89.7 or 89.01) have been reported. Moreover, the proportion of patients who experienced infection, underwent surgery or had both was also computed. IBD-related surgical interventions (proctocolectomy surgery) were identified by the ICD-9-CM procedural codes (45.3X, 45.4X, 45.6X, 45.7X, 45.8X, 45.9X, 46.0X, 46.1X, 46.2X, 46.3X, 46.6X, 46.7X, 48.0X, 48.1X, 48.3X, 48.4X, 48.5X, 48.6X, 48.7X, 48.8X, 48.9X, 49.0X, 49.1X, 49.3X, 49.5X, 49.6X, 49.7X), and infection were detected by the presence of prescriptions of antibacterials for systemic use (ATC J01).

A prediction of the number of patients expected to start biologicals in the 5 years subsequent the study was computed considering the amount of UC or CD diagnoses in 2019 with reference to the percentage of patients eligible to biologics found between 2015 and 2019.

2.4. Statistical analysis

Continuous variables were reported as mean and standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Percentages of patients potentially eligible for biological therapy were referred to the proportion of patients with one or more criteria among patients not treated with this therapy. All statistical analyses were performed using STATA SE, version 17.0 (StataCorp LLC, College Station,TX, USA).

3. Results

Among a study sample covering approximately 11.3% of the overall Italian population, 26,781 patients diagnosed with IBD were identified, considering all available periods in the database (Fig. 1). Based on the treatment received or not during the drug utilization period, 8517 (corresponding to 31.8% of the overall cohort) were untreated, and 18,264 (corresponding to 68.2% of the overall IBD population) were treated; among them, 3125 (11.7%) were bio-treated, and 15,139 (56.5%) were defined as non-bio-treated (Fig. 1). Moreover, in the group of the 3125 bio-treated patients, 670 (21.4%) experienced infection, 224 (7.2%) underwent surgery, and 722 (23.1%) had both. Browsing the drug prescriptions through the ATC codes, it was found that 952 out of 3125 patients (30.5%) received more than one biological drug, 246 (7.9%) more than two, and the remaining part received only one biological drug type.

Data re-proportioned to the Italian population at the study period (N = 60,111,989) estimated in this analysis a total of 236,744 patients affected by IBD; 161,454 patients were treated (27,625 with biologicals while 133,829 were non-bio-treated) and 75,290 IBD patients resulted to be without medication during the last year (Fig. 1).

After applying eligibility criteria for biologicals, overall, 7651 IBD patients (28.6% of our sample corresponding to 67,635 patients in Italy) met at least one of the 5 criteria but were untreated with biological drugs during the last recent year. These patients, thus defined potentially eligible for biologics, resulted from the sum of 4770 patients (17.8%, corresponding to 42,167 patients by the Italian estimation) who received therapies other than biologics (non-bio-treated) and 2881 patients (10.8%, corresponding to 25,468 patients by the Italian projection) without any medication (untreated) (Fig. 1).

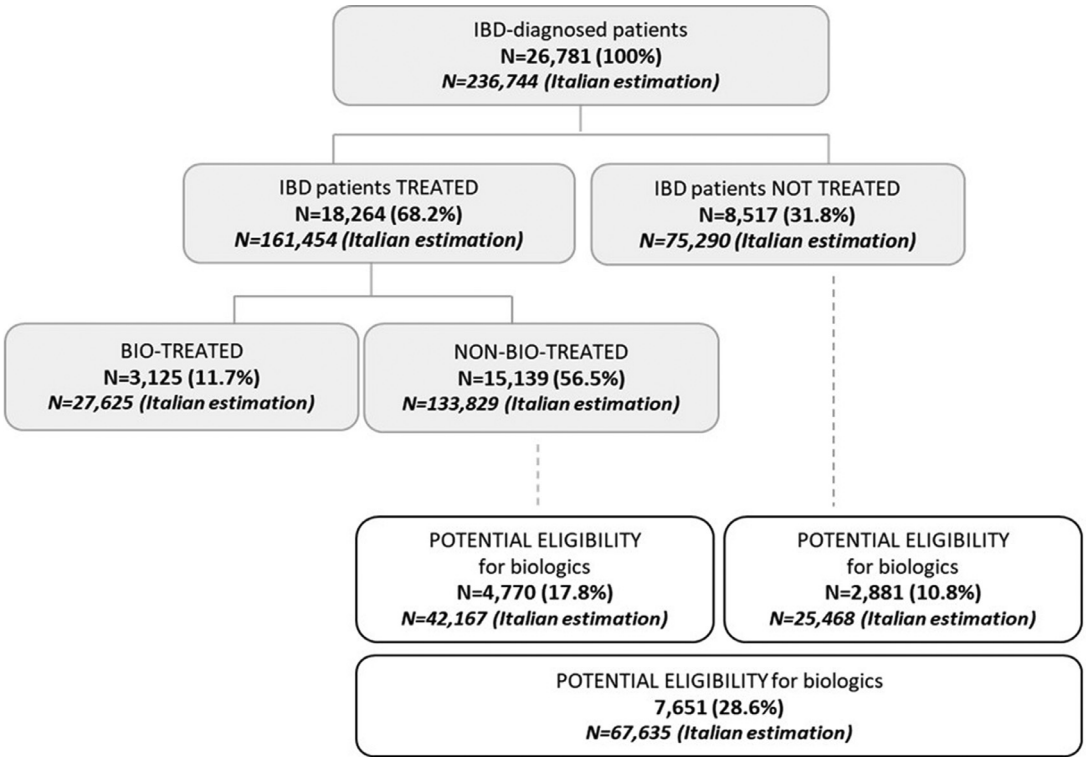

Fig. 1. Patients' identification and potential eligibility to iologic agents among study population and data estimation to Italian population.

Table 2
Distribution of patients potentially eligible for biological therapy according to criteria applied. Data are expressed as numbers and percentages in brackets.

	IBD patients Non-bio-treated $N = 15{,}139$	IBD patients Not treated $N = 8517$
Patients potentially eligible to biologics	4770 (17.8%)	2881 (10.8%)
Patients eligible by criterion A	55 (1.2%)	8 (0.3%)
Patients eligible by criterion B	2756 (57.8%)	767 (26.6%)
Patients eligible by criterion C	319 (6.7%)	187 (6.5%)
Patients eligible by criterion D	2660 (55.8%)	2205 (76.5%)
Patients eligible by criterion E	558 (35.8%)	299 (25.6%)

Despite the criteria were not mutually exclusive (since a patient could present more than one criteria), among non-bio-treated patients, 57.8% were described as steroid-dependent patients (by criterion B), 55.8% met the criterion D as having a severe relapsing disease (Table 2 and Supplementary Table 1), 35.8% were defined CD patients with highly active disease and poor prognosis (by criterion E), 6.7% of patients were intolerant or contraindicated to conventional therapies, and 1.2% were defined potentially eligible by having steroid-refractory active disease (by criterion A) (Table 2 and Supplementary Table 1). Among IBD untreated patients potentially eligible for biologics, 26.6% met the steroid-dependency criteria (by criterion B), 76.5% met the criterion D for as having the severe relapsing disease, 25.6% were CD patients with highly active disease and poor prognosis (by criterion E), and 6.5% were defined as having a severe relapsing disease (by criterion C) (Table 2 and Supplementary Table 1). IBD untreated and never treated patients were 52% and 57.3% males with ages at the inclusion of 54.5 ± 18.8 and 53.9 ± 20.1 years (Supplementary Table 2). Moreover, 42.5% and 36.8% of untreated patients had previous IBD hospitalization and gastrointestinal examination, respectively (Supplementary Table 2). In IBD patients never treated, 43% presented IBD hospitalization and 16.5% a prescription for gastrointestinal examination during the period before the index date (Supplementary Table 2).

The patients potentially expected to start biologicals in the 5 year-period following the study was calculated on the basis of the number of UC or CD diagnoses in 2019 and the percentage of patients eligible to biologics found between 2015 and 2019. Using this approach, 376 (29.0%) IBD patients have been estimated to start biological therapy in 2019, 386 (29.8%) in 2020, 368 (28.4%) in 2021, 352 (27.2%) in 2022, and 367 (28.3%) in 2023.

4. Discussion

During the last 25 years, the introduction of biologics represented an important step forward in the therapeutic management of IBD. It has been reported that in patients with moderate-to severe disease, these drugs are effective in promoting both the induction and a maintenance of clinical and endoscopic remission [22], with the reduction in inflammatory markers [23], lowering the risk of surgery in patients with IBD [24], and to reduce the risk of hospitalization [25]. Data from the real-world settings showed that the majority of IBD patients did not receive biologics during their clinical history or received them during the late phase of the disease [26,27].

This administrative claims-based observational analysis provided an overview of IBD patients' therapeutic management in Italy, giving and estimation at National level of patients who are potentially eligible for biological drugs and not yet currently treated with these agents. To assess eligibility, five criteria were applied based on guidelines and available literature for the therapeutic management of IBD patients [11,18–21]. Almost 27,000 patients with IBD diagnosis have been identified, corresponding 236,744 patients by Italian estimation. Our findings showed a tendency of undertreatment among IBD patients, with almost 30% of patients (almost 75,300 patients estimated in Italy) being without medication, and with only 11% of patients being treated with bio-

logicals, during the most recent year of the database availability. It has been widely reported that biologic therapy remains underutilized among IBD patients, with the majority of patients not receiving them or starting the treatment during the late phase of the disease [28], despite several evidence support that an early therapeutic approach based on biologicals might be associated with more favourable outcomes [29–31].

At present, the scarcity of similar RWE analyses focused on the underuse of biological therapy in potentially eligible IBD patients prevents us from making a really fitting comparison with literature data of other countries. Most of the currently available RWE published papers rather evaluated clinical outcomes or safety and effectiveness profiles of biologics vs conventional therapies (i.e. steroids) or between biologicals with different mechanism of action (i.e. anti-TNF drugs vs anti-interleukin drugs) [32–35]. However, a large real-world study on 415,405 patients in US investigated outpatient IBD drug utilization trends during a 9-year period from 2007 to 2015. In spite of the relative minority of biologic-treated patients compared to other drug classes, like 5-ASAs, immunomodulators and corticosteroids, the authors reported an increasing utilization of biologics, specifically from 21.8% to 43.8% for CD and 5.1%−16.2% for UC [17]. This markedly larger recourse to biological therapies for IBD observed in the American study, compared to our data, might be feasibly explained by their earlier introduction in US (infliximab is the first FDA-approved TNF inhibitor since 1998) [29] and their wider spectrum of available biologics (namely adalimumab, certolizumab pegol, golimumab, infliximab, natalizumab, vedolizumab, ustekinumab), compared to those currently approved in Italy by AIFA (Italian Medicine Agency) [9,10].

The application of potential eligibility criteria among IBD patients untreated with biologicals estimated that 28% of them, corresponding to an overall of 67,635 patients in Italy, presented one or more potential eligibility criteria for biologic therapies. In particular, more than 50% of patients under conventional treatments met the criteria for being steroid-dependent or with the severe disease with relapse, identified by corticosteroid dose increase and IBD-related hospitalization [11,19–21]. The percentage of IBD relapsing patients increased to almost 70% among untreated patients. Previous population-based studies have suggested that approximately 50% of patients with IBD experienced corticosteroids during their clinical history, and up to 10% use them once a year [36]. It has been reported that exists a significant burden of corticosteroid use among the IBD population related to drug complications [37–40]; moreover, in a US population-based study, it has been reported over two-thirds of patients being exposed within 10 years of diagnosis, with 3% to 5% of long-term IBD patients using corticosteroids at any time. Heavy use of corticosteroid early in the disease is a strong predictor of both the continued use of heavy corticosteroids and the need for resection surgery [40].

The biological underuse phenomenon observed in the present analysis could be related to several factors. Siegel et al. found in a cross-sectional study that patients perceived corticosteroids as more beneficial, familiar, and less dreadful than biologics [41], and in a recent analysis carried out in real-world settings reported that the apparent underuse of biologicals could be related to physicians' concerns about costs, and on the treatment tolerability and contraindications [42].

The present results must be interpreted by taking into account the limitations related to the observational nature of the analysis, which was based on data collected from administrative databases. Our cohort of patients reflected real clinical practice by evaluating data from a sub-set of health-assisted individuals. In addition, there was a lack or limited clinical information on disease severity, comorbidities, and other potential confounders that could have influenced the present results. Moreover, it was impossible to gain information from administrative databases on the reasons behind the underuse of biological drugs, which could be related to clinical reasons or to the adopted treatment strategies.

In conclusion, this real-world data analysis conducted at National level, estimated the number of patients with a diagnosis of IBD patients and evaluate their therapeutic management. Our results highlighted a tendency to undertreatment with the biological agents among CD and UC patients, and over one-fourth of patients, not currently treated with biologicals, were considered potentially eligible to these drugs, mainly due to their extensive use of steroids or the presence of disease relapse. These data suggest that an unmet medical need exists among the Italian general clinical practice for managing patients affected by IBD.

Author contributions

Luca Degli Esposti: Conceptualization, Resources, Visualization, Supervision; **Valentina Perrone:** Conceptualization, Data curation, Writing –review & editing; **Diego Sangiorgi:** Data curation, Statistical analysis, Methodology; **Stefania Saragoni:** Methodology; Data curation; **Melania Dovizio:** Writing – first draft, review & editing, Data curation, Methodology, Visualization; **Flavio Caprioli:** Conceptualization, Visualization, Revision; **Fernando Rizzello**: Conceptualization, Visualization, Revision; **Marco Daperno:** Conceptualization, Visualization, Revision; **Alessandro Armuzzi:** Conceptualization, Visualization, Revision.

Declaration of Competing Interest

Flavio Caprioli served as consultant to: Abbvie, MSD, Takeda, Janssen, Roche, Celgene, Bristol-Meyers Squibb, Galapagos, Gilead, Pfizer, Mundipharma, Galapagos, Biogen, Ferring. He received lecture fees from Abbvie, Ferring, Takeda, Allergy Therapeutics, Janssen, Pfizer, Biogen, and unrestricted research grants from Giuliani, Sofar, MSD, Takeda, Abbvie, Celltrion, Pfizer. All the other coauthors have no competing interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.04.022.

References

[1] Chang JT. Pathophysiology of inflammatory bowel diseases. N Engl J Med 2020;383(27):2652–64.
[2] Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. World J Gastroenterol 2014;20(1):91–9.
[3] GBD 2017 Inflammatory Bowel Disease CollaboratorsThe global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020;5(1):17–30.
[4] Ng Siew C, HY Shi, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2017;390(10114):2769–78.
[5] Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. Scand J Gastroenterol 2015;50:942–51.
[6] Irvine EJ. Quality of life of patients with ulcerative colitis: past, present, and future. Inflamm Bowel Dis 2008;14:554–65.
[7] Bodger K. Cost of illness of Crohn's disease. Pharmacoeconomics 2002;20:639–52.
[8] Ward FM, Bodger K, Daly MJ, et al. Clinical economics review: medical management of inflammatory bowel disease. Aliment Pharmacol Ther 1999;13:15–25.
[9] Macaluso FS, Orlando A, Papi C, et al. Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD); Working panel; Review panel. Use of biologics and small molecule drugs for the management of moderate to severe ulcerative colitis: IG-IBD clinical guidelines based on the GRADE methodology. Dig Liver Dis Apr 2022;54(4):440–51. doi:10.1016/j.dld.2022.01.127.
[10] Macaluso FS, Papi C, Orlando A, et al. Italian group for the study of inflammatory bowel disease (IG-IBD); working panel; review panel. Use of biologics for the management of Crohn's disease: IG-IBD clinical guidelines based on the GRADE methodology. Dig Liver Dis Feb 13 2023 S1590-8658(23)00166-4. doi:10.1016/j.dld.2023.01.155.

[11] Orlando A, Armuzzi A, Papi C, et al. Italian society of gastroenterology; italian group for the study of inflammatory bowel disease. The Italian society of gastroenterology (SIGE) and the Italian group for the study of inflammatory bowel disease (IG-IBD) clinical practice guidelines: the use of tumor necrosis factor-alpha antagonist therapy in inflammatory bowel disease. Dig Liver Dis Jan 2011;43(1):1–20.
[12] Raine T, Bonovas S, Burisch J, et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. J Crohns Colitis Jan 28 2022;16(1):2–17.
[13] Colombel JF, Narula N, Peyrin-Biroulet L. Management strategies to improve outcomes of patients with inflammatory bowel diseases. Gastroenterology 2017;152:351–61.
[14] Kim S, Koh SJ. Corticosteroid, a double-edged sword in inflammatory bowel disease management: possibility of reducing corticosteroid use through physician education. Intest Res Oct 2022;20(4):389–91.
[15] Ferrari L, Krane MK, Fichera A. Infammatory bowel disease surgery in the biologic era. World J Gastrointest Surg 2016;8(5):363–70.
[16] Privitera G, Pugliese D, Lopetuso LR, Scaldaferri F, Neri M, Guidi L, Gasbarrini A, Armuzzi A. Novel trends with biologics in inflammatory bowel disease: sequential and combined approaches. Therap Adv Gastroenterol Apr 27 2021;14:17562848211006669.
[17] Yu H, MacIsaac D, Wong JJ, et al. Market share and costs of biologic therapies for infammatory bowel disease in the USA. Aliment Pharmacol Ther 2018;47(3):364–70.
[18] Gomollón F, Dignass A, Annese V, et al. ECCO. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. J Crohn's Colitis Jan 2017;11(1):3–25 d.
[19] Davis KL, Wang E, Dastani H, et al. Treatment patterns, complications, and disease relapse in a real-world population of moderate-to-severe ulcerative colitis patients initiating immunosuppressive therapy. Gastroenterology 2013;144(5) S-642-S-643.
[20] Bots SJ, Kuin S, Ponsioen CY, et al. Relapse rates and predictors for relapse in a real-life cohort of IBD patients after discontinuation of anti-TNF therapy. Scand J Gastroenterol Mar 2019;54(3):281–8.
[21] Beaugerie L, Seksik P, Nion-Larmurier I, et al. Predictors of Crohn's disease. Gastroenterology Mar 2006;130(3):650–6.
[22] Hazlewood GS, Rezaie A, Borman M, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. Gastroenterology 2015;148(2) 344-54 e5; quiz e14-15.
[23] Jahnsen J, Detlie TE, Vatn S, et al. Biosimilar infliximab (CT-P13) in the treatment of inflammatory bowel disease: a Norwegian observational study. Expert Rev Gastroenterol Hepatol 2015;Suppl 1:45–52.
[24] Tsai L, Ma C, Dulai PS, Prokop LJ, et al. Contemporary risk of surgery in patients with ulcerative colitis and Crohn's disease: a meta-analysis of population-based cohorts. Clin Gastroenterol Hepatol Oct 2021;19(10) 2031-2045.e11.
[25] Mao EJ, Hazlewood GS, Kaplan GG, et al. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther 2017;45(1):3–13.
[26] Targownik LE, Tennakoon A, Leung S, et al. Temporal trends in initiation of therapy with tumor necrosis factor antagonists for patients with inflammatory bowel disease: a population-based analysis. Clin Gastroenterol Hepatol 2017;15 1061-1070.e1.
[27] Siegel CA, Yang F, Eslava S, et al. Treatment pathways leading to biologic therapies for ulcerative colitis and Crohn's disease in the United States. Clin Transl Gastroenterol 2020;11:e00128.
[28] Berg DR, Colombel JF, Ungaro R. The role of early biologic therapy in inflammatory bowel disease. Inflamm Bowel Dis 2019;25:1896–905.
[29] Rawla P, Sunkara T, Raj JP. Role of biologics and biosimilars in inflammatory bowel disease: current trends and future perspectives. J Inflamm Res May 16 2018;11:215–26.
[30] Papamichael K, Cheifetz AS, Melmed GY, Irving PM, Vande Casteele N, Kozuch PL, Raffals LE, Baidoo L, Bressler B, Devlin SM, Jones J, Kaplan GG, Sparrow MP, Velayos FS, Ullman T, Siegel CA. Appropriate therapeutic drug monitoring of biologic agents for patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol Aug 2019;17(9) 1655-1668.e3.
[31] De Felice KM. Patients Perception of Risks and Benefits of Biologic Therapy. Inflamm Bowel Dis Jan 1 2020;26(1):147–9.
[32] Bokemeyer B, Plachta-Danielzik S, Di Giuseppe R, et al. German inflammatory bowel diseases study group (GISG). Real-world comparative effectiveness of ustekinumab vs Anti-TNF in Crohn's disease with propensity score adjustment: induction phase results from the prospective, observational RUN-CD study. Inflamm Bowel Dis Jan 12 2023:izac271.
[33] Lin WC, Tai WC, Chang CH, et al. Real-world evidence of effectiveness and safety of vedolizumab for inflammatory bowel disease in taiwan: a prospective nationwide registry (VIOLET) study. Inflamm Bowel Dis Jan 10 2023:izac269.
[34] Zhuleku E, Antolin-Fontes B, Borsi A, et al. Real-world outcomes associated with switching to anti-TNFs versus other biologics in Crohn's Disease patients: a retrospective analysis using German claims data. Therap Adv Gastroenterol Nov 4 2022;15:17562848221130554. doi:10.1177/17562848221130554.
[35] Rubín de Célix C, Chaparro M, Gisbert JP. Real-world evidence of the effectiveness and safety of ustekinumab for the treatment of Crohn's disease: systematic review and meta-analysis of observational studies. J Clin Med Jul 20 2022;11(14):4202.
[36] Loftus EV Jr, Schoenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. Aliment Pharmacol Ther 2002;16:51–60.
[37] Benchimol EI, Seow CH, Steinhart AH, et al. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2008:CD006792.
[38] Hoes JN, Jacobs JW, Verstappen SM, et al. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis 2009;68:1833–8.
[39] Targownik LE, Nugent Z, Singh H, et al. Prevalence of and outcomes associated with corticosteroid prescription in inflammatory bowel disease. Inflamm Bowel Dis Apr 2014;20(4):622–30.
[40] Curtis JR, Westfall AO, Allison J, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum 2006;55:420–6.
[41] Siegel CA. Review article: explaining risks of inflammatory bowel disease therapy to patients. Aliment Pharmacol Ther 2011;33:23–32.
[42] Cohn HM, Dave M, Loftus EV Jr. Understanding the cautions and contraindications of immunomodulator and biologic therapies for use in inflammatory bowel Disease. Inflamm Bowel Dis Aug 2017;23(8):1301–15.