Acta Farmacêutica Portuguesa
2025 vol. 14, n.1, pp.3-17

Description of real-world treatment patterns of advanced therapies for Inflammatory Bowel Disease in Portugal

Descrição de vida real dos padrões de tratamento de terapêuticas avançadas para a Doença Inflamatória Intestinal em Portugal

Alves D.[1], Prata R.[1]

ARTIGO ORIGINAL | ORIGINAL ARTICLE

RESUMO

A doença inflamatória intestinal (DII) é uma doença imunológica complexa. As terapêuticas biológicas são a chave para o tratamento da DII moderada a grave em doentes que falham ou são intolerantes ao tratamento convencional. No entanto, existem alguns doentes para os quais, para manter uma resposta adequada, é necessário ajustar a frequência das terapêuticas em relação ao que está aprovado ou recomendado no resumo das características do produto.

O objetivo deste estudo foi descrever retrospetivamente os padrões de tratamento de vida real das terapêuticas avançadas para a DII em Portugal durante a fase de manutenção do tratamento, utilizando dados de uma base de dados nacional de dispensa de medicamentos, entre abril de 2017 e fevereiro de 2022.

Foram incluídos 4.200 doentes seguidos em 18 hospitais portugueses. Nas terapêuticas avançadas de primeira linha, 53,7% dos doentes estavam em infliximab, 28,6% em adalimumab, 12,6% em vedolizumab, 3,7% em ustecinumab, 1,2% em golimumab e 0,2% em tofacitinib. 756 doentes (18,0%) mudaram para outra terapêutica avançada (segunda linha). Dos doentes que estavam em primeira linha e mudaram, 38% estavam a tomar golimumab, 21,4% a vedolizumab, 19,7% a adalimumab, 17,1% a infliximab e 1,3% a ustecinumab. Verificou-se que mais de 70% de todas as terapêuticas avançadas foram dispensadas de acordo com o intervalo de dispensa previsto. Em 10,3% dos doentes tratados com infliximab e 23,7% tratados com ustecinumab, os medicamentos foram dispensados com maior frequência.

Mais de 80% dos doentes com DII moderada a grave foram tratados com uma terapêutica anti-TNF-α na primeira linha. Na segunda linha, a maioria estava a tomar ustecinumab ou vedolizumab. Apesar de mais de 70% dos doentes terem dispensado o medicamento, aproximadamente ¼ dos doentes tratados com ustecinumab têm uma maior frequência de dispensa de medicamentos, mostrando que a escalada da dose pode ter um papel na prática clínica portuguesa.

Palavras-chave: doença inflamatória intestinal, terapia avançada, tratamento de vida real, dispensa de fármacos.

ABSTRACT

Inflammatory bowel disease (IBD) is a complex immunologic condition. Biological therapies are the key to managing moderate to severe IBD in patients who fail or are intolerant to conventional treatment. There are some patients for whom, to maintain an appropriate response, it is necessary to adjust the frequency of the therapies for each patient compared to what is approved or recommended in the summary of product characteristics.

The goal of this study was to describe real-world treatment patterns of advanced therapies for IBD in Portugal during the maintenance treatment phase, using data from a drug dispensing nationwide database. This was a retrospective study that included a cohort from a patient-level hospital dispensing a Portuguese database of advanced therapies for IBD between april 2017-february 2022.

4200 patients followed in 18 Portuguese hospitals were included. In the first-line advanced therapies, 53.7% of the patients were on infliximab, 28.6% on adalimumab, 12.6% on vedolizumab, 3.7% on ustecinumab, 1.2% on golimumab and 0.2% in tofacitinib. 756 patients (18.0%) switched to another advanced therapy (second line). Of the patients that were in first-line and switched, 38% were on golimumab, 21.4% on vedolizumab, 19.7% on adalimumab, 17.1% on infliximab, and 1.3% on ustecinumab. More than 70% of all advanced therapies were dispensed according to the expected dispensing interval. 10.3% of the patients treated with infliximab and 23.7% treated with ustecinumab dispensed the drugs more frequently.

More than 80% of the patients with moderate to severe IBD were treated with anti-TNF-α therapy in the first-line. Most of the patients were on ustecinumab or vedolizumab in the second line. Although more than 70% of the patients had their drug dispensed, approximately ¼ of the patients treated with ustecinumab have a higher frequency of drug dispensing, showing that dose escalation could have a role in the Portuguese clinical practice.

Keywords: Inflammatory bowel disease, advanced therapies, real-world treatment, drug dispensing.

[1]Abbvie, Lda. Estrada de Alfragide, 67, Edifício D. 2610-008 Amadora. Portugal.

Corresponding author: Diana Alves; diana.alves@abbvie.com. Address: Abbvie, Lda. Estrada de Alfragide, 67, Edifício D, 2610-008 Amadora, Portugal

Submetido/Submitted: 29 de janeiro de 2025| Aceite/Accepted: 10 de abril de 2025

 ISSN: 2182-3340

INTRODUCTION

Inflammatory bowel disease (IBD) is a complex immunologic condition characterized by chronic intestinal inflammation that comprises ulcerative colitis (UC) and Crohn's disease (CD)[1]. Signs and symptoms of active IBD may include abdominal pain, rectal bleeding, diarrhea, and fatigue[2]. This is a disease with a typical relapsing and remitting course that requires long-term medical treatment in the majority of patients[3].

In Europe, 2 million people suffer from the IBD and, in Portugal, the incidence of CD varies from 3.77 to 6.38 per 100,000 person-years (1990-2016) and UC ranges from 4.98 to 7.71 per 100,000 person-years (1990-2016)[4].

Current treatment options include mesalazine [5-Aminosalicylic acid (5ASA)] or similar, steroids, immunosuppressors and biologic therapy, such as antitumor necrosis factor (anti-TNF) (adalimumab, infliximab, golimumab), anti-integrin drugs (vedolizumab), anti-interleukin (IL)12 and IL-23 (ustecinumab), and Janus Kinase inhibitors (tofacitinib)[1]. Biological therapies are the cornerstone for the management of moderate to severe IBD in patients who fail or are intolerant to conventional treatment[5].

In order to achieve and/or maintain an appropriate response, the administration of biological therapy for each patient compared to what is recommended in the summary of product characteristics (SmPC) can vary[6,7]. There is often an increase or shortening of the dosing interval from the initial recommended starting maintenance dose[8].

Due to this dose variation, it is difficult to determine the real cost of biological therapies to the healthcare system. Therefore, to appropriately characterize IBD advanced therapies in the real-world setting, it is critical to understand local treatment patterns.

There is one available study[9] that included data from an IBD Portuguese cohort. However, this study does not reflect or correlate the impact of treatment patterns on disease management and its costs, nor does it describe the real-world treatment patterns of advanced therapies for IBD in Portugal.

This study aims to describe real-world treatment patterns of advanced therapies for IBD in Portugal during the maintenance treatment phase, using data from a drug dispensing nationwide database in Portugal.

METHODS

Study design

Retrospective cohort analysis using a drug dispensing nationwide Portuguese database of patient-level hospital dispensing data of advanced therapies for IBD. For each drug of interest (adalimumab, vedolizumab, infliximab, ustecinumab, golimumab, and tofacitinib – Table 1), and only for the maintenance phase, patients were followed up from the first prescription fill according to a medical prescription, until treatment discontinuation or end of the study period. The dispensing data were collected between april 2017 and february 2022.

Drug discontinuation was identified when: 1) the time gap between 2 periods of supply exceeds twice the average time of supply of the 3 previous dispensing records. When less than 3 previous dispensing records exist, the shortest administration time recommended in the SmPC were considered; 2) no sufficient periods of supply were previously dispensed to cover that gap.

Table 1. Drugs of interest, loading doses and expected maintenance dose administration schedules

Generic name	Dose administration schedules	Expected dispensing records per one period of supply	Strength and presentation
Adalimumab [10]	40mg EOW	2x40mg PFP per month	40 mg/PFP or 80 mg/PFP
	40mg EW	4x40mg PFP per month	
	80mg EOW	2x80mg PFP per month	
Golimumab [11]	50mg Q4W	1x50mg PFP per month	50 mg/PFP
	100mg Q4W	1x100mg PFP per month	
Infliximab [12]	5mg/kg Q8W	4 vials per 2 months	100 mg/vial
	10mg/kg Q8W	8 vials per 2 months	
Tofacitinib [13]	5mg BID	56 tablets per month	5 mg/tab or 10mg/tab
	10mg BID		
Ustecinumab [14]	90mg Q12W	1X90mg PFS per 3 months	90 mg/PFS
	90mg Q8W	1X 90mg PFS per 2 months	
Vedolizumab [15]	300mg Q8W	1X 300mg vial per 2 months	300 mg/vial
	300mg Q4W	1X 300mg vial per month	

Legend: PFP: pre-filled pen; PFS: pre-filled syringes, BID: twice a day; EOW: every other week; EW: every week; Q4W: every four weeks; Q8W: every eight weeks; Q12W: every twelve weeks.

Data source

The drug dispensing nationwide Portuguese database (from Health Market Research company, HMR) collects data both from pharmacies, mass market and hospital sources. A webservice is used to collect, anonymize (using a standard anonymization algorithm approved by the Portuguese National Commission of Data Protection), and send the anonymized and encrypted data to drug dispensing nationwide Portuguese database. In a hospital point of view, HMR database includes patient-level drug dispensing data from 42% of all Portuguese National Health System hospitals, representing 86% of the drug consumption in value.

This database has information regarding the patients' age, but no other demographic or clinical data are available, therefore, it is not possible to differen-

tiate treatments prescribed for Crohn's Disease from those for Ulcerative Colitis or indeterminate Colitis. Despite this, dispensing of all advanced therapies for IBD is usually recorded by all hospitals in the cost center "gastro". Exceptions from this procedure may arise when patients have a hospital admission into another service (e.g., surgery), and in these cases, drugs originally prescribed by gastro may be recorded in other cost centers. Therefore, data for a specific patient are eligible to be analyzed in this study, if the mode of cost center for the individual patients is "gastro" (which includes all prescriptions by gastroenterologists). In this context, it is assumed that a residual number of patients with no significant impact in the final results of this study, will have the IBD advanced therapies prescribed out of the "gastro" cost center scope.

The drug dispensing nationwide Portuguese database has a contract with the hospitals that allows the utilization and publication of data if confidentiality and anonymization of the data source are maintained. For this reason, data can only be presented as aggregated.

The average dosing interval is calculated by dividing the treatment time by the number of dispensations, e.g., if a patient treated with adalimumab has a treatment time of 21 months and has a total number of 21 consumptions in that same period, then was considered an average of 1 administration per month (q1M). Therefore, q2M and q3M were defined as treatments administered every two months or three months, respectively (on average).

To calculate the treatment costs for each available supplier, the average of the unit costs per dosage was considered.

Eligibility criteria

Inclusion criteria: 1) IBD drugs of interest: adalimumab, golimumab, infliximab, tofacitinib, ustecinumab and vedolizumab; 2) initiation of a drug of interest for IBD between april 2017 – february 2022; 3) at least 4 refills during 12 consecutive months; 4) individual patients whose drug dispensing cost center is "gastro".

Exclusion criteria: 1) patients with combinations of 2 or more different advanced treatments for the same supply period; 2) patients only with records of drugs returned to the hospital pharmacy.

The exclusion criteria were adapted during the analysis performed, based on the protocol and HMR database.

Considering the treatment interval, patients were excluded if it was the first treatment of each drug to account for the induction period and patients with drugs with only one month of consumption. However, patients can be repeated more than once because HRM considers specific treatment periods in each patient.

Outcomes

1) Proportion of patients by line of individual therapy: usage in 1st, 2nd, 3rd, etc. lines during the observation period were investigated through the proportion of patients that were maintained on the first treatment option and those that were switched to other treatments; 2) proportion of patients who were on each advanced therapy and switched therapy: treatment dispensing over time was investigated using counts and proportions of patients with dispensing records for each drug of interest over time; 3) proportion of patients on a specific dose schedu-

le of an advanced therapy: dose and administration schedules of the dispensed drugs of interest were investigated using counts and proportions; 4) proportion of patients that experienced dose escalation or reduction: treatment escalation was investigated using counts and proportions of patients with at least one dose increase, or shortening of average dosing interval, compared to the expected dosing schedule as presented in Table 1. The mean time to first dose escalation/reduction was also considered. The mean time to treatment switching was also considered.

Statistical analysis

Counts and proportions were estimated for the categorical baseline characteristics and outcomes (i.e., dose pattern categories, dose, and dose escalation). Mean, minimum and maximum were used to describe continuous outcomes (i.e., number of vials/pre-filled syringes, time to dose escalation).

RESULTS

Study Population

This study included 4,200 patients followed in 18 Portuguese hospitals (6 hospitals in the North, 3 in the Centre and 9 in the South). Most of the patients were from the North (52.4%), followed by the South (31.4%) and by the Center of the country (16.3%). Regarding age distribution, 46.9% of the patients were between 15-39 years, 35.6% were 40-59, 15.8% were 60-79, 1.1% were more than 80 years, and only 0.6% were less than 15 years.

Overall proportion of patients in each advanced and switch therapy

Figure 1 represents the proportion of patients in each advanced therapy. It is observed that 53.7% of the patients started advanced therapies with infliximab and 28.6% with adalimumab. In second-line 36.1% of the patients were on ustecinumab and 22.0% on vedolizumab. Ustecinumab was dispensed in 49.1% and 47.1% of the patients in third and fourth lines, respectively.

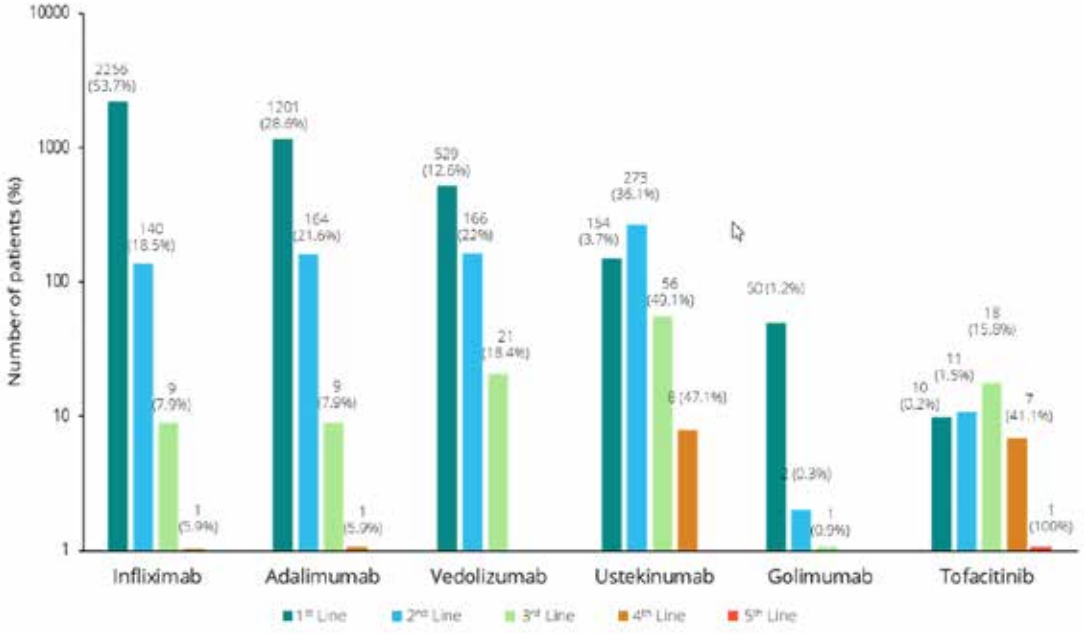

Figure 1. Number and percentage of patients in each advanced therapy and treatment lines.

Switches between lines of therapy

Of the 4,200 patients included in this study, 3,042 (72.4%) remained in first line therapy until the end of data collection, 402 (9.6%) discontinued first-line therapy and 756 (18.0%) switched to other advanced therapy (second line). Within the patients that switched to a second-line therapy, 75.5% remained in this therapeutic line until the end of data collection, 9.4% discontinued the drug, and 15.1% switched to other advanced therapy (third line), representing 2.7% of the total number of patients. Seventeen patients (14.9%) switched to the fourth line of advanced therapy. In this line, which includes only 0.4% of the total number of patients, 1 patient switched to fifth line and 1 discontinued the drug (Figure 2).

Proportion of patients that switched from first to second line therapy

In Figure 3, in dark blue, is represented the percentage of patients in each advanced therapy (first-line) that switch to a second-line. Of the patients that were in first-line and switched, 38% were on golimumab, 21.4% on vedolizumab, 19.7% on adalimumab, 17.1% on infliximab, and 1.3% on ustecinumab. In adalimumab, golimumab and ustecinumab (first-line), 41.5%, 57.9% and 100% of the patients switched to second-line infliximab, respectively. Almost 42% of the patients on second line adalimumab switched from first line infliximab (Figure 3).

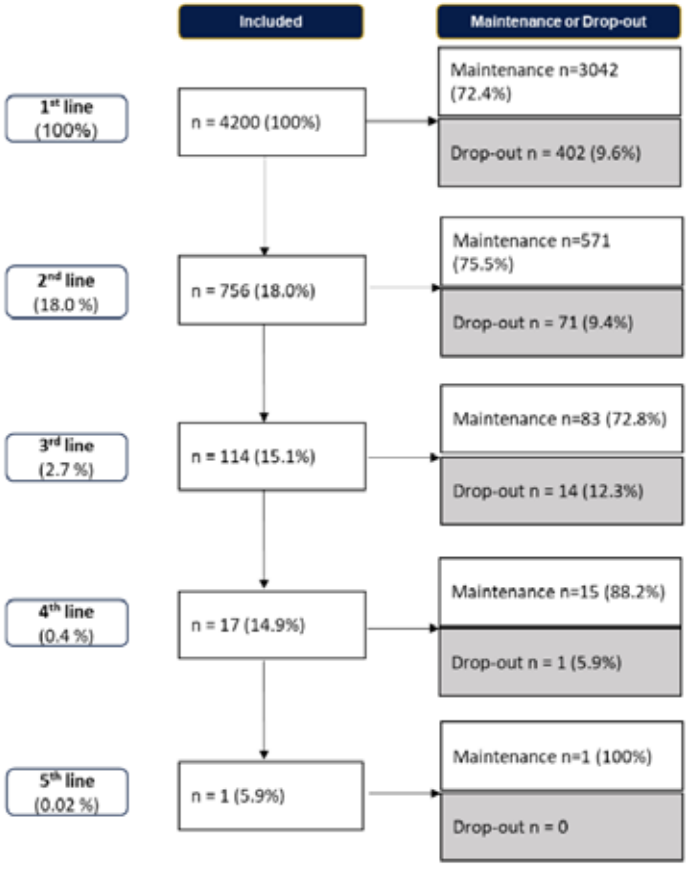

Figure 2. Overview of switches between lines.

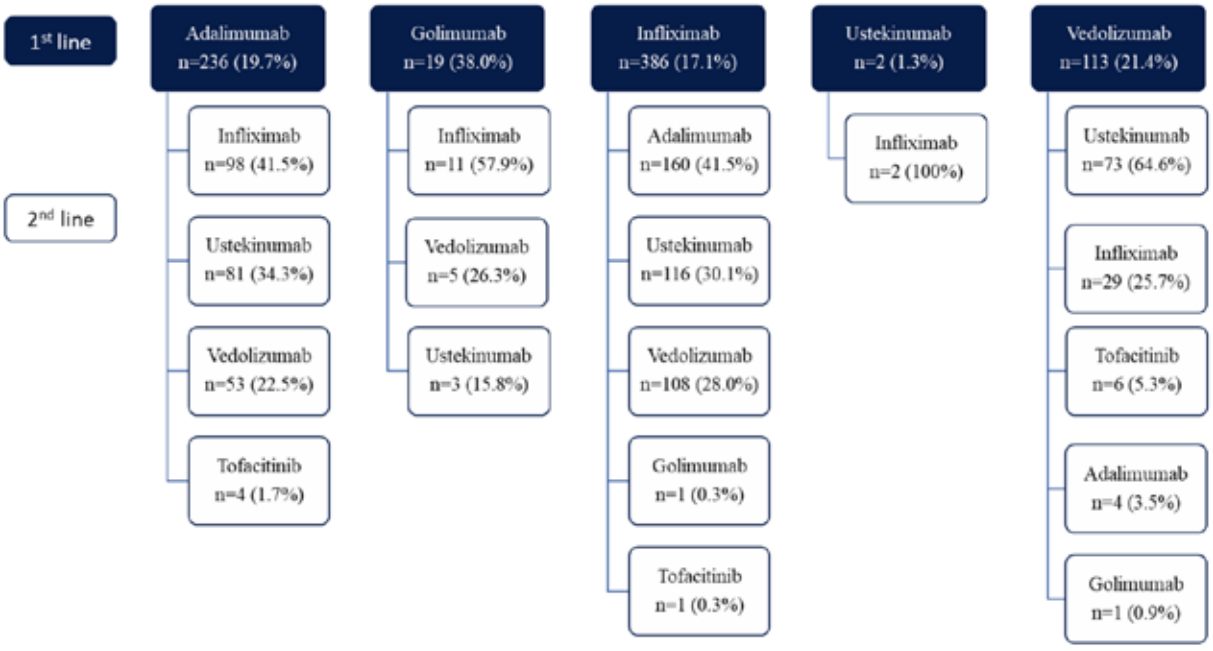

Figure 3. Overview of switches between first and second line, specifying the switch molecule from-to.

Proportion of patients that switched from second to third line therapy

In Figure 4, in dark blue, is represented the percentage of patients in each advanced therapy that switch from second-line to third-line. Infliximab presented a switch corresponding to 25.7%, vedolizumab to 21.7%, adalimumab to 16.5%, and ustecinumab to 5.1%. Ustecinumab was the drug chosen for the third line in patients from adalimumab (55.6%), infliximab (61.1%) and vedolizumab (52.8%) in second-line. Approximately 36% of the patients treated with ustecinumab in second-line therapy switched to tofacitinib (Figure 4).

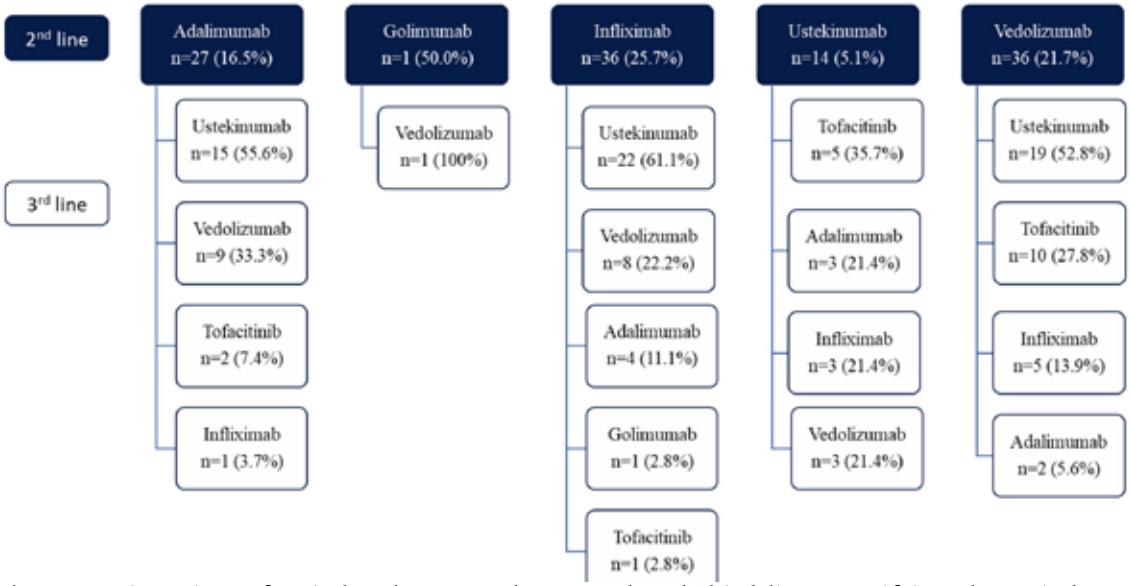

Figure 4. Overview of switches between the second and third line, specifying the switch molecule from-to.

Treatment time until switch, in each line and in each advanced therapy

Patients remained a mean of 15.57 months in first line adalimumab until the switch to other therapeutic option. The mean time until the switch in infliximab was 13.88 months.

From the second to the third line, the mean time before the switch in adalimumab and vedolizumab was 12.93 months and 12.74 months, respectively. In vedolizumab the mean time until the switch was 11.6 months (Table 2).

Table 2. Treatment time until switch, in each line and in each advanced therapy

Drug	Switch	Mean treatment time until switch (months)	Min treatment time until switch (months)	Max treatment time until switch (months)
Adalimumab	1st - 2nd line	15.57	1.02	53.95
Adalimumab	2nd - 3rd line	12.93	1.94	38.01
Adalimumab	3rd - 4th line	0.99	0.99	0.99
Golimumab	1st - 2nd line	10.13	2.99	25.04
Infliximab	1st - 2nd line	13.88	0.99	50.04
Infliximab	2nd - 3rd line	8.48	1.02	22.01
Infliximab	3rd - 4th line	3.02	3.02	3.02
Ustecinumab	1st - 2nd line	14.05	5.03	23.06
Ustecinumab	2nd - 3rd line	7.69	1.02	19.02
Ustecinumab	3rd - 4th line	8.76	4.04	11.99
Ustecinumab	4th -5th line	5.03	5.03	5.03
Vedolizumab	1st - 2nd line	12.21	0.99	34.99
Vedolizumab	2nd - 3rd line	12.74	2.96	34.00
Vedolizumab	3rd - 4th line	11.59	5.98	18.00

Proportion of patients who experienced dose escalation or reduction

Figure 5 represents the proportion of patients in the different schedules of dose dispensing in each advanced therapy. More than 70% of all advanced therapies were dispensed according to the expected dispensing interval (SmPC and Table 1). Table 3 includes the dosing interval, compared to the expected dosing schedule in each advanced therapy.

For adalimumab, the mean dispensing interval of the drug was 1.8 months in 10.9% of the patients and 1.1 months in 89.1% of the patients (Figure 5 and Table 3). Similar results were found for golimumab. For infliximab, it was found that in 10.3% of the patients the dispensing interval was numerically inferior to what was expected (mean of 1.3 months vs 1.9 months, respectively) (Figure 5 and Table 3). The expected dispensing of tofacitinib occurred in 100% of the patients. Ustecinumab and vedolizumab had two expected intervals of dispensing (Table 1). Specifically, for ustecinumab, 3.8% of the patients had a dispensing interval of q3M (Q12W),

superior than expecting, 72.5% of q2M (Q8W) or q3M, and 23.7% had an inferior dispensing interval, reflecting that these patients could have a higher dose of treatment when compared with the base dosage of q3M (Q12W).

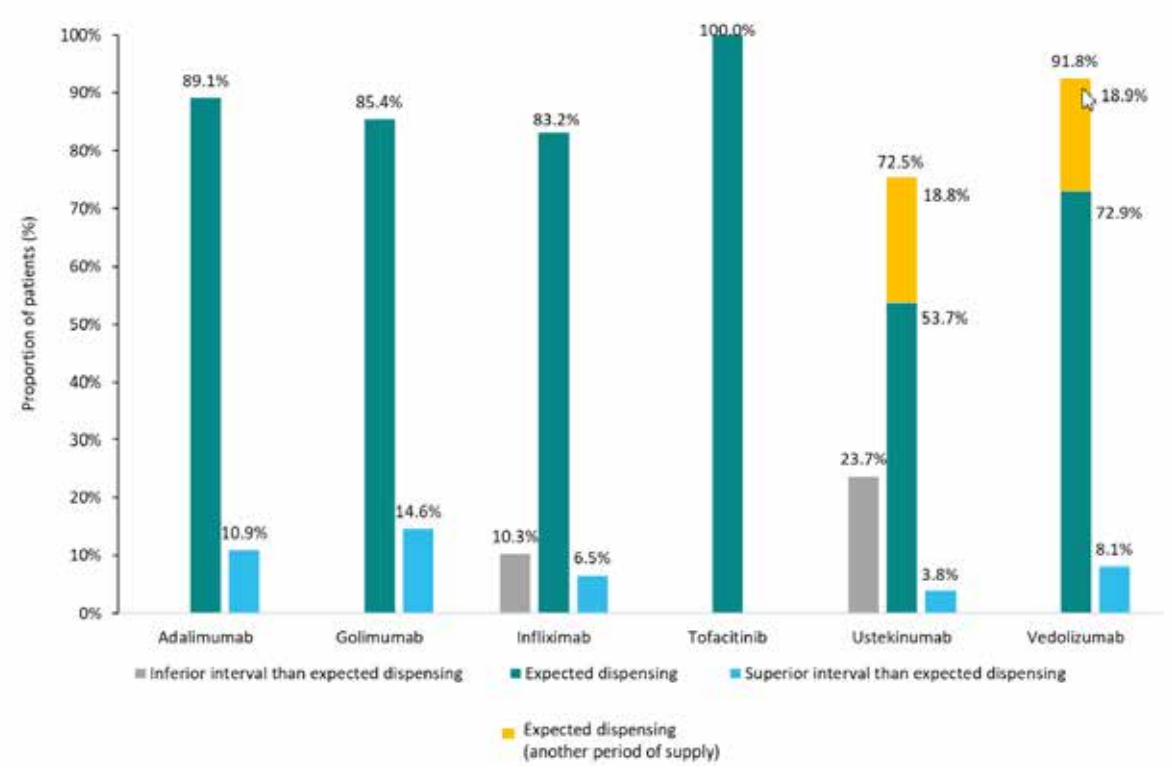

Figure 5. Proportion of patients in each advanced therapy and intervals of drug dispensing. Ustecinumab and vedolizumab have two expected dosing intervals represented in green and yellow; ustecinumab: green – q2M, yellow – q3M; vedolizumab: green – q2M, yellow – q1M

Table 3. Dosing interval, compared to the expected dosing schedule in each advanced therapy

Drug	Dispensing records (per one period of supply)	Mean treatment interval (months)	Minimum treatment interval (months)	Maximum treatment interval (months)
Adalimumab	Expected dispensing (q1M)	1.1	1.0	1.4
	Superior interval than expected dispensing	1.8	1.5	3.0
Golimumab	Expected dispensing (q1M)	1.1	1.0	1.4
	Superior interval than expected dispensing	1.8	1.5	2.0

Table 3. Dosing interval, compared to the expected dosing schedule in each advanced therapy (cont.)

Infliximab	Inferior interval than expected dispensing	1.3	1.0	1.4
	Expected dispensing (q2M)	1.9	1.5	2.4
	Superior interval than expected dispensing	3.0	2.5	7.0
Tofacitinib	Expected dispensing (q1M)	1.0	1.0	1.0
Ustecinumab	Inferior interval than expected dispensing	1.7	1.1	1.9
	Expected dispensing (q2M)	2.1	2.0	2.4
	Expected dispensing (q3M)	2.7	2.5	3.0
	Superior interval than expected dispensing	4.0	3.2	5.0
Vedolizumab	Expected dispensing (q1M)	1.2	1.0	1.4
	Expected dispensing (q2M)	1.9	1.5	2.4
	Superior interval than expected dispensing	3.1	2.5	7.0

Legend: q1M, every month; q2M, every 2 months; q3M, every 3 months; q4M, every 4 months.

Doses and costs

Almost 100% of the patients in adalimumab had the dispensed dose of 40mg regardless of the dispensing interval. Regarding golimumab, 59.4% of the patients in q1M were dispensed with a 100mg dose, and in the > q1M interval, this dose was dispensed in 95% of the patients. In infliximab, ustecinumab and vedolizumab, only one dose was available. In tofacitinib, most patients (73.5%) had the dispensed dose of 5mg. Table 4 also includes the price per month for each drug, considering the different dispensing intervals and the number of dispensed packages.

Table 4. Dose and number of packages dispensed for each drug and corresponding price per month

Drug	Dispensing interval	Dose, mg	Packages dispensed (n%)	Price/month of dispensed drug (€)
Adalimumab	q1M	40	51,463 (97.6)	12,091,091.5
		80	1,084 (2.1)	303,520.0
	> q1M	40	3,515 (97.8)	400,937.5
		80	78 (2.2)	10,920.0
Golimumab	q1M	100	527 (59.4)	352,742.2
		50	360 (40.6)	240,962.4
	> q1M	100	109 (95.6)	36,479.0
		50	5 (4.4)	1,673.4
Infliximab	< q2M	100	22,495 (99.5)	8,544,680.8
	q2M	100	118,396 (99.7)	22,486,241.9
	> q2M	100	3158 (100.0)	389,534.12
Tofacitinib	q1M	10	6,642 (26.5)	146,161.9
		5	18,383 (73.5)	202,266.3
Ustecinumab	< q2M	90	1164 (99.6)	4,674,810.24
	q2M-q3M	90	1922 (98.2)	3,859,529.76
	> q3M	90	58 (100.0)	58,234.32
Vedolizumab	q1M- q2M	300	7882 (100.0)	6,785,998.0
	> q2M	300	255 (100.0)	6,380.3

Legend: q1M, every month; q2M, every 2 months; q3M, every 3 months; q4M, every 4 months.

DISCUSSION

In therapy for moderately to severe active IBD, treatment escalation with an anti-TNF therapy, vedolizumab, or tofacitinib is required in patients who required two or more corticosteroid courses in the previous year, or who become corticosteroid-dependent or refractory[16]. The choice of drug should be determined by clinical factors, patient choice, cost, potential for adherence, and local infusion ability[16]. Therefore, in most cases, the treatment of patients with IBD does not fit perfectly into any specific set of guidelines[7].

In this study, we found that infliximab and adalimumab (anti-TNF-α therapies) were numerically more dispensed as first line than other advanced therapies. This is in line with the literature, since anti-TNF-α are the most frequent biologic drugs used in first-line[1] to treat patients who are intolerant or do not respond well to corticosteroids or are steroid-dependent[16]. In fact, up to 40% of patients do not respond to anti-TNF-α, and nearly 20-46% of patients experience secondary failure one year after anti-TNF-α treatment[6]. In our study, 15.3% of patients failed anti-TNF-α therapy and, from all advanced therapies, 18% of patients failed to respond (primary or secondary failure) to first line therapy.

In patients failing an optimized anti-TNF-α dosing regimen, the next step is usually to switch to another anti-TNF agent or to another class, such as using vedolizumab, an anti-integrin antibody, or ustecinumab, an antibody against the p40 subunit of both IL-12 and IL-23[17]. These steps are concordant with what was observed in this study, with patients in an anti-TNF-α regimen (adalimumab, infliximab or golimumab) switching to another anti-TNF-α drug. Patients on ustecinumab or vedolizumab often switched to infliximab and ustecinumab, respectively. The mean time until switch from the first to the second line was numerically superior in adalimumab, followed by ustecinumab, infliximab, vedolizumab and golimumab, with a range between 10.1 and 15.6 months.

Ustecinumab and vedolizumab were numerically more dispensed in the second and third lines. This is in line with what was observed in other studies[6]. Infliximab, vedolizumab and adalimumab had a numerically higher percentage of patients that needed a switch to 3rd line. Patients on adalimumab, infliximab or vedolizumab switched frequently to ustecinumab, reinforcing the use of this drug in second and third line[6]. As observed in the switch from first to second line and in the switch from second to third line, adalimumab was the advanced therapy on which the patients remained numerically longer before switching (12.9 months), whilst ustecinumab showed a numerically shorter time until switch (7.7 months). In this study, and regardless of the drug, the higher the line of treatment the lower the mean treatment time until switch, numerically. As reported in the literature, the number of prior treatments is negatively associated with therapeutic success, and biologic-naive patients have a substantially higher likelihood of responding to treatment in IBD[18,19].

Ustecinumab and vedolizumab have reported response rates of 40-70% and loss of response (LOR) rates of approximately 20-30% in the first year[6]. In our study, failure of vedolizumab was apparently similar to what is referred in the literature. However, for ustecinumab, LOR was frequently lower during the duration of this study. It is important to underline that LOR to a subsequent second-class biologic is frequent[6].

Strategies for managing the loss of response or achieving long-term remission include dose escalation and reducing dosing interval (3, 6 In this cohort, more than 70% of the patients had the therapy dispensed in the expected period. According to the ECCO Guidelines on Therapeutics in UC[20], although appropriate dose escalation or dose optimization can play a role in clinical practice, there are minimal high-quality trial data in this field, and uncontrolled studies are subject to several potential forms of bias. For this reason, ECCO has restricted recommendations to the doses studied in randomized clinical trials). However, in this real-world data, it was found that in ustecinumab, 23.7% of the patients had a dispensed in a superior interval of the expected. This result was found in other studies, where patients required dose escalation to every four weeks (q1M), with inflammation achieving complete remission and response in 38% and 31%, respectively[21] or successful in maintaining clinical response in 61.1% of patients[22].

There are no publications regarding the cost of each drug in Portuguese cohorts, which hampers understanding of the true cost of the escalation and reducing dosing interval in IBD patients.

Although different doses of each drug were dispensed, the most dispensed dose of each drug was the same regardless of the different dispensing intervals, except for tofacitinib.

This study has several limitations: 1) no diagnosis information is available in the used database and, therefore, it was not possible to identify cases of CD and UC, despite having an identical prevalence[23]; 2) it is not possible to guarantee that all dispensed drugs were actually administered to the patients; 3) dispensing data is available per month, and it may not accurately reflect drugs administered in time intervals that are not multiples of 1 month (e.g. administration every 6 weeks); 4) drug quantity used in the dosing evaluation was based on quantities available in retrospective data sources, which can present limitations for products billed in vials; 5) results for this study reflect those included in the database and may not represent exactly the intended dosing as prescribed by physicians; 6) results for this study should be carefully interpreted since they may not be generalizable beyond the study sample, and sample size may be limited for newer products with lower prescription rates; 7) there were no data to respond to the outcome mean time to first dose escalation/reduction.

The strengths of this study are the number of patients included (n=4,200) and the fact that the drug dispensing nationwide Portuguese database used collects data directly from 42% of all Portuguese NHS hospitals, representing 86% of the national drug consumption costs.

CONCLUSIONS

In this study, more than 80% of the patients were in an anti-TNF-α therapy in first line, and the majority of the patients used ustecinumab or vedolizumab in second line. The higher the line of treatment the lower the mean treatment time until switch, numerically. More than 70% of the patients had their drug dispensed as expected according to SmPC. However, in ustecinumab, 23.7% of the patients had a dispensing in superior interval of the expected. Therefore, dose escalation or dose optimization can play a role in clinical practice, this includes patients who lose response with the dosing specified by default, and who may benefit from an increase in the dosing frequency for shorter time interval in line to SmPC.

ACKNOWLEDGEMENTS

Professional medical writing, editorial assistance, and statistical evaluation of the data were provided by the scientific company x2 Science Solutions (x2SS).

Conflict of interests: All authors are employees of Abbvie. No other relationships/ conditions/ circumstances that present a potential conflict of interest.

Funding: The study was supported by Abbvie, Lda.

REFERENCES

1. Zaltman C, Parra RS, Sassaki LY, Santana GO, Ferrari MLA, Miszputen SJ, et al. Real-world disease activity and sociodemographic, clinical and treatment characteristics of moderate-to-severe inflammatory bowel disease in Brazil.

World J Gastroenterol. 2021;27(2):208-23.

2. Vilela EG, Torres HO, Martins FP, Ferrari Mde L, Andrade MM, Cunha AS. Evaluation of inflammatory activity in Crohn's disease and ulcerative colitis. World J Gastroenterol. 2012;18(9):872-81.

3. Moens A, Verstockt B, Alsoud D, Sabino J, Ferrante M, Vermeire S. Translating Results from VARSITY to Real World: Adalimumab vs Vedolizumab as First-line Biological in Moderate to Severe IBD. Inflamm Bowel Dis. 2022;28(8):1135-42.

4. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, 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. Eriksson C, Rundquist S, Lykiardopoulos V, Udumyan R, Karlén P, Grip O, et al. Real-world effectiveness of vedolizumab in inflammatory bowel disease: week 52 results from the Swedish prospective multicentre SVEAH study. Therap Adv Gastroenterol. 2021;14:17562848211023386.

6. Albshesh A, Taylor J, Savarino EV, Truyens M, Armuzzi A, Ribaldone DG, et al. Effectiveness of Third-Class Biologic Treatment in Crohn's Disease: A Multi-Center Retrospective Cohort Study. J Clin Med. 2021;10(13).

7. Armuzzi A, DiBonaventura MD, Tarallo M, Lucas J, Bluff D, Hoskin B, et al. Treatment patterns among patients with moderate-to-severe ulcerative colitis in the United States and Europe. PLoS One. 2020;15(1):e0227914.

8. Argollo M, Kotze PG, Kakkadasam P, D'Haens G. Optimizing biologic therapy in IBD: how essential is therapeutic drug monitoring? Nat Rev Gastroenterol Hepatol. 2020;17(11):702-10.

9. Magro F, Portela F, Lago P, Chagas C, Moreira F, Pereira F, et al. Burden of Disease and Cost of Illness of Inflammatory Bowel Diseases in Portugal. GE - Portuguese Journal of Gastroenterology. 2022.

10. EMA. European Medicines Agency. Humira 20 mg solution for injection in pre-filled syringe. 2009 [updated 11/10/2022] Available from: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf

11. EMA. European Medicines Agency. Simponi 45 mg/0.45 mL solution for injection in pre-filled pen. 2009 [updated 09/11/2021] Available from: https://www.ema.europa.eu/en/documents/product-information/simponi-epar-product-information_en.pdf

12. EMA. European Medicines Agency. Remicade 100 mg powder for concentrate for solution for infusion. 2013 [updated 28/09/2022] Available from: https://www.ema.europa.eu/en/documents/product-information/remicade-epar-product-information_en.pdf

13. EMA. European Medicines Agency. Xeljanz 5 mg and 10 mg film-coated tablets. 2017 [updated 28/09/2022] Available from: https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf

14. EMA. European Medicines Agency. Stelara 130 mg concentrate for solution for infusion. 2009 [updated 15/11/2022] Available from: https://www.ema.europa.eu/en/documents/

product-information/stelara-epar-product-information_en.pdf

15. EMA. European Medicines Agency. Entyvio 300 mg powder for concentrate for solution for infusion. 2014 [updated 11/10/2022] Available from: https://www.ema.europa.eu/en/documents/product-information/entyvio-epar-product-information_en.pdf

16. Okobi OE, Udoete IO, Fasehun OO, Okobi T, Evbayekha EO, Ekabua JJ, et al. A Review of Four Practice Guidelines of Inflammatory Bowel Disease. Cureus. 2021;13(8):e16859.

17. Cai Z, Wang S, Li J. Treatment of Inflammatory Bowel Disease: A Comprehensive Review. Front Med (Lausanne). 2021;8:765474.

18. Verstockt B, Mertens E, Dreesen E, Outtier A, Noman M, Tops S, et al. Influence of Drug Exposure on Vedolizumab-Induced Endoscopic Remission in Anti-Tumour Necrosis Factor [TNF] Naïve and Anti-TNF Exposed IBD Patients. J Crohns Colitis. 2020;14(3):332-41.

19. Feagan BG, Lasch K, Lissoos T, Cao C, Wojtowicz AM, Khalid JM, et al. Rapid Response to Vedolizumab Therapy in Biologic-Naive Patients With Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2019;17(1):130-8.e7.

20. Raine T, Bonovas S, Burisch J, Kucharzik T, Adamina M, Annese V, et al. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. J Crohns Colitis. 2022;16(1):2-17.

21. Honap S, Meade S, Ibraheim H, Irving PM, Jones MP, Samaan MA. Effectiveness and Safety of Ustecinumab in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. Dig Dis Sci. 2022;67(3):1018-35.

22. Kopylov U, Afif W, Cohen A, Bitton A, Wild G, Bessissow T, et al. Subcutaneous ustecinumab for the treatment of anti-TNF resistant Crohn's disease-the McGill experience. J Crohns Colitis. 2014;8(11):1516-22.

23. Azevedo LF, Magro F, Portela F, Lago P, Deus J, Cotter J, et al. Estimating the prevalence of inflammatory bowel disease in Portugal using a pharmaco-epidemiological approach. Pharmacoepidemiol Drug Saf. 2010;19(5):499-510.