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Safety, Efficacy and Persistence of Advanced Therapies in Inflammatory Bowel Disease: Results from ORIGINS. A Retrospective Observational Study

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ABSTRACT

Background & Aims: Real-world assessments of efficacy and safety of advanced therapies used for inflammatory bowel disease (IBD) patients are limited. We aimed to report safety, efficacy and treatment persistence of new molecules (infliximab, adalimumab, vedolizumab, tofacitinib, ustekinumab) in a retrospective multicentric national Romanian analysis.

Methods: We conducted a nationwide, retrospective observational multicentric study. Data were collected retrospectively from electronic and paper files. Patients who started on one of the five investigated molecules during December 2019-December 2021 were included. The main outcome measures were clinical remission, endoscopic healing, persistence on treatment and safety data.

Results: A total of 678 adult patients from 24 Romanian IBD centers with a diagnosis of ulcerative colitis or Crohn's disease were included. Participants had previously failure to one (268, 39.5%), two (108, 15%) or more treatment lines and only 38% (259) were biologic naïve. In the 24 months study period, most patients were started on vedolizumab (192, 28%), followed by adalimumab, infliximab, ustekinumab and tofacitinib. In biologic-naïve patients, most physicians (72%) preferred anti-TNF treatment as first line biologic (93 patients started on infliximab, 92 on adalimumab), followed by vedolizumab, ustekinumab and tofacitinib. During follow-up, 71% (470, p=0.05) of patients achieved clinical remission and 36% (134, p=0.03) achieved mucosal healing. The 6 months milestone for persistence was reached in 78% (530) of cases. Almost half of patients (47%, 316 patients) persisted on their current treatment for over 12 months. Overall, an adverse reaction was reported for 67 (10.4%) patients, with no lethal events.

Conclusions: Population of biologic-experienced IBD patients in Romania is increasing and is becoming more difficult to achieve long-term disease control. Discontinuation rates for advanced therapies are high.

Key words: inflammatory bowel disease – biologics – treatment persistence – advanced therapies – efficacy – safety.

Abbreviations: ADA: adalimumab; anti-TNF: tumor necrosis factor antagonist; CD: Crohn's disease; IBD: inflammatory bowel disease; IFX: infliximab; TOFA: tofacinitib; UC: ulcerative colitis; USTEK: ustekinumab; VDZ: vedolizumab.

INTRODUCTION

After the approval of tumor necrosis factor antagonists (anti-TNFs) for IBD treatment two decades ago, several other biologic and small molecule drugs became available. We are now witnessing a change in the management paradigm, with vedolizumab (VDZ) [1, 2], ustekinumab (USTEK) [3] and tofacinitib (TOFA) [4, 5] making new advances in achieving treatment goals for inflammatory bowel disease (IBD) patients. Real-world assessment of efficacy and safety of these new treatment options, especially comparative analyses, are just now beginning to emerge [6-8]. Additionally, few high-quality studies compared so far these molecules, in terms of achieving treatment goals and further providing the data to be implemented in international society guidelines and clinical practice. Considering the heterogenicity of studies and patients, it is easy to understand why objective, reproducible measures are obstacles difficult to surmount. At the present, the hiatus of high-quality evidence makes choosing from the available

medical therapies, especially in biologic naïve patients, a challenge.

Persistence on treatment is a newly used measure, highly reproducible and easier to report than usual clinical and endoscopic disease activity scores that can serve as a useful proxy for treatment efficacy. Medication persistence, defined as the time (months) from drug initiation to discontinuation of therapy, has been suggested as a surrogate for real-world therapeutic benefit and safety [9, 10].

We aimed to report safety, efficacy and treatment persistence of advanced treatment options [infliximab (IFX), adalimumab (ADA), VEDO, TOFA, USTEK] in a retrospective multicentric national Romanian analysis.

METHODS

We conducted a nationwide, retrospective observational multicentric study. An invitation to participate was extended to all Romanian IBD Centers. The study was conducted according to the STROBE Statement.

Study Population

Patients over 18-year old diagnosed with Crohn's disease (CD) or ulcerative colitis (UC) were considered for this analysis. Data were collected retrospectively from electronic and paper files. Patients started on one of the five investigated molecules (IFX, ADA, VEDO, USTEK, TOFA) during December 2019-December 2021 were included. If patients were started on more than one molecule during the study period, the most recent treatment option was recorded as "current treatment" and previous therapies were recorded in the medication history section. Patients that were already treated with one of the mentioned therapies in December 2019 or were started on one after December 2021 were not included in our study.

Data Collection

Investigators collected data regarding patient baseline characteristics (gender, age, smoking status), disease (extension, phenotype, duration), history of surgery for IBD, previous treatments (exposure to azathioprine/ADA/IFX/TOFA/USTEK/VEDO), duration and reason for treatment cessation (lack of response, loss of response, adverse event, deep remission, other reason). The main focus of data collection was set on three different aspects: a) current treatment (IFX, ADA, VEDO, USTE, TOFA), duration and need for concomitant corticosteroids; b) safety data: adverse events (serious infection, opportunistic infection, hospitalization, life-threatening event, worsening of IBD or extraintestinal manifestations, cancer, surgery, death, severe allergic reaction) and course of action (continuation/cessation of treatment); c) treatment outcomes: clinical remission and endoscopic healing as well as persistence on treatment.

Clinical remission was defined as the return to baseline characteristics (normal stool frequency, absence of rectal bleeding, absence of abdominal pain or weight loss).

Endoscopic healing assessment was based on the evaluator decision. Absence of ulcerations (for both UC and CD) or Mayo score of 0/1, Simple Endoscopic Score for Crohn's Disease (SES-CD) <3 were suggested for endoscopic healing. Endoscopic outcomes were recorded in our analysis if colonoscopy was done after treatment initiation but was not older than 12 months.

Medication persistence was defined as the time from drug initiation to discontinuation of therapy.

Serious infection was defined as an infectious event requiring hospitalization.

Study design and data collection flow-chart is available in Fig. 1.

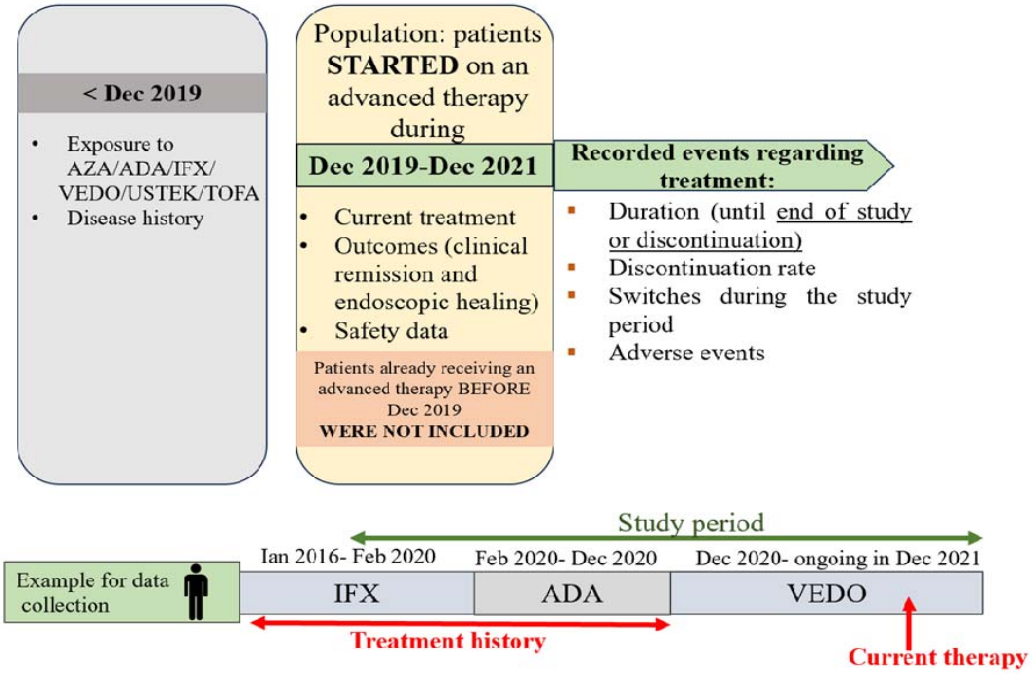

Fig. 1. Study flow-chart.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 20.0 for Windows (IBM Corp., Armonk NY,USA). Data analysis included descriptive statistics computed for continuous variables, expressed as mean and standard deviation (SD). Categorical variables were described as counts and percentages and compared by the Chi-Squared test unless 25% of the cells had expected counts of less than 5, in which case Fisher's exact test was employed. Demographics and disease classification between groups were compared with a Chi-square test. Logistic regression analysis was used to determine factors associated with treatment persistence of biologics. A p-value <0.05 was considered statistically significant.

RESULTS

In total, 678 adult patients from 24 Romanian IBD Centers with a diagnosis of UC or CD were included in the final analysis. Patient baseline characteristics are summarized in Table I.

Table I. Patient baseline characteristics

Age (years, SD)	39 (± 14.2)
Gender (male), n (%)	323 (55)
Diagnosis (UC/CD), n (%)	305/373 (45/55)
Disease extension, n (%)	
E1/E2/E3	28/122/155 (9/40/51)
L1/L2/L3/L4	86/103/184/19 (23/28/49/5)
Smoker, n (%)	133 (21)
Phenotype, n (%)	
B1/B2/B3/p	148/165/60/83 (39/44/16/22)
Previous IBD surgery, n (%)	119 (17)
Disease duration (years, SD)	6 (±5)

B1: inflammatory; B2: stricturing; B3: penetrating; CD: Crohn's disease; E1: proctitis; E2: left colitis; E3: pancolitis; L1: ileal; L2: colonic; L3: ileocolonic; L4: upper gastrointestinal involvement, p: perianal disease; SD: standard deviation; UC: ulcerative colitis;.

Previous Treatments

Previous exposure to azathioprine, other biologic (IFX, ADA, USTEK, VEDO) or small molecule (TOFA) was recorded, and results are listed in Fig. 2. Almost half of patients (311, 45%) received prior to their current treatment azathioprine (alone or in combination with infliximab).

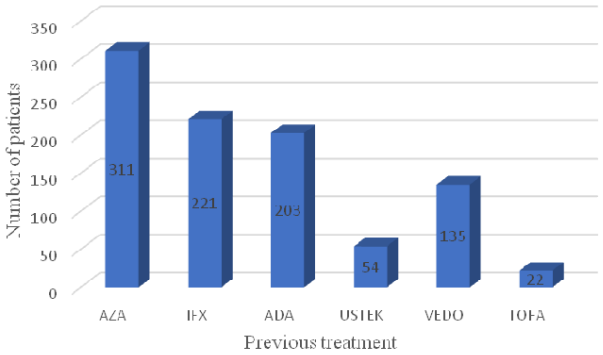

Fig. 2. Previous exposure to advanced therapies.

From the total of 678 patients started on one of the five investigated molecules, 268 (39.5%), have previously failed to one, 108 (15%) failed to two investigated molecules (Fig. 3). Only 259 (38%) were biologic naïve prior to initiation of current therapies.

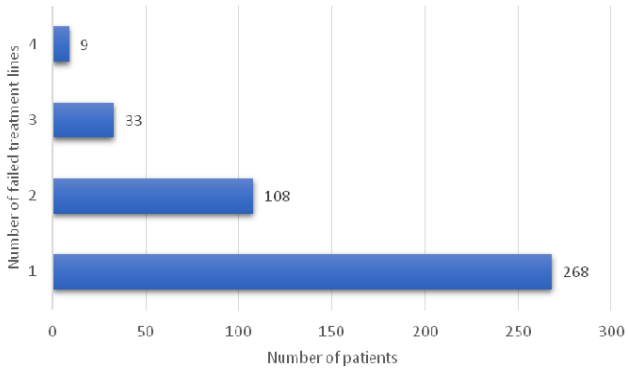

Fig. 3. Patient experience with advanced therapies.

The main reason for treatment discontinuation was loss of response, followed by initial lack of response or adverse events. In two patients treated with anti-TNF agents the reason for treatment discontinuation was deep remission (Table II). Deep remission was defined as sustained clinical remission, endoscopic and histologic healing (>12 months).

Table II. Reasons for treatment discontinuation

Reason for treatment discontinuation (n, %)	IFX	ADA	VEDO	USTEK	TOFA
Lack of response	44 (23)	49 (28)	23 (48)	4 (36)	4 100)
Loss of response	111 (58)	108 (63)	23 (48)	7 (63)	0 (0)
Adverse reaction	31 (16)	12 (7)	1 (2)	0 (0)	0 (0)
Other	4 (2)	0 (0)	0 (0)	0 (0)	0 (0)

ADA: adalimumab; IFX: infliximab; TOFA: tofacinitib; USTEK: ustekinumab; VDZ: vedolizumab.

Current Treatments

In the 24 months study period, most patients were started on VEDO (192, 28%), followed by ADA, IFX, USTEK and TOFA (Fig. 4). For patients started on VEDO, 44% (107) of them had previously failed an anti-TNF agent. At the time of enrollment in our study, 18 patients treated with one of the investigated molecules during December 2019-December 2021 were enrolled in a clinical trial or had no ongoing treatment.

In biologic-naïve patients, the majority of physicians (72%) preferred anti-TNF treatment as first line biologic (93 patients started on IFX, 92 on ADA), followed by VEDO, USTEK and TOFA.

For ongoing molecules (started during the study period), the median duration of follow-up was 10 months (highest for VEDO with a median of 12 months, followed by adalimumab, with a median duration of 11 months) (Fig. 5). Patients started on USTEK had the shortest median time of follow-up on treatment, of 7 months.

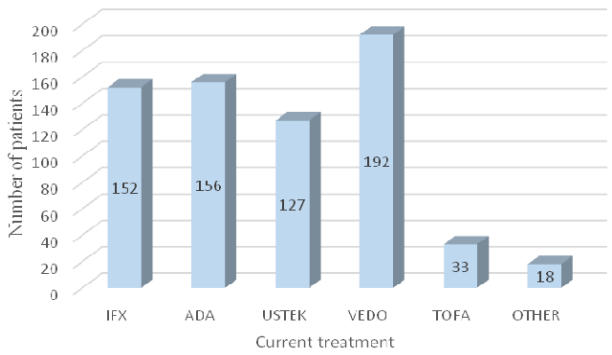

Fig. 4. Frequency of initiation for investigated molecules during the 24 months study period.

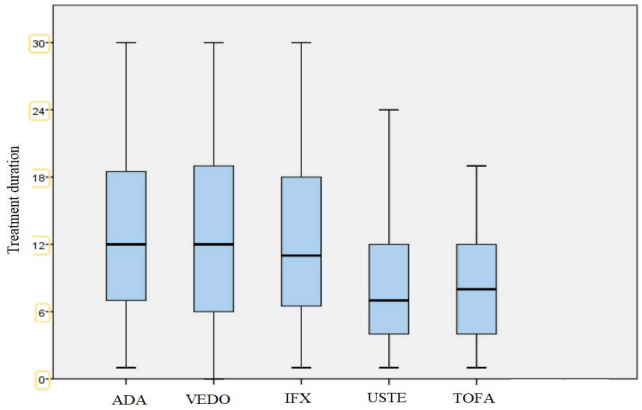

Fig. 5. Duration of follow-up on current treatments.

Patients started in the last 24 months on a new treatment (one of the five investigated molecules) reached the 6 months milestone for persistence in 78% (530) of cases and almost half of patients (47%, 316 patients) were persistent on their current treatment for over 12 months.

On multivariable analysis, CD and ongoing corticosteroids were associated with persistence on treatment at 6 months. Disease duration, CD, active smoking and concomitant use of corticosteroids were associated with persistence on treatment at 12 months.

For ongoing treatments, we assessed usual treatment targets recommended by guidelines [11] (clinical remission and mucosal healing) (Fig. 6). During follow-up, 71% (470, p=0.05) of patients achieved clinical remission and 36% (134, p=0.03) achieved mucosal healing. A recent (<12 months) endoscopic evaluation was, however, available only in 54% (367) of patients. Irrespective of chosen treatment, the proportion of responders (expressed as clinical remission) was significantly higher than the rate of non-responders (clinically active disease during follow-up) (p<0.001). Rates of clinical remission and mucosal healing for each molecule can be consulted in Table IV. Only a small proportion of patients (84, 12%) were receiving concomitant corticosteroid therapy at the time of outcome assessment.

Table IV. Treatment outcomes for current therapies

Molecule	Patients in clinical remission (%)	Patients with mucosal healing (if endoscopy was available) (%)
IFX	68%	32%
ADA	70%	40%
VEDO	77%	42%
USTEK	61%	21%
TOFA	66%	43%

For abbreviations see Table II.

A direct statistical comparison of efficacy between the investigated molecules was not possible with the available heterogenous data.

Discontinued Treatments

For the 678 enrolled patients we recorded history of exposure to advanced therapies. Given the longer market availability of anti-TNF, most patients (340, 50%) previously exposed to advanced therapies, received an anti-TNF agent, of which 84 (24%) received both IFX and ADA.

From the total of 221 IFX-exposed patients, 101 (45%) discontinued the medication by 12 months of follow-up. The median treatment duration was 14 months, with only 42 (19%) achieving long-term persistence on treatment (>36 months).

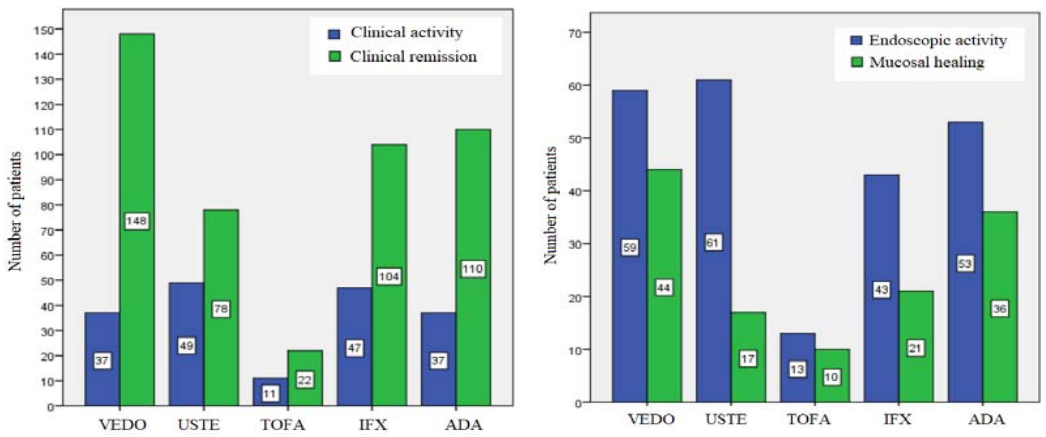

Fig. 6. Outcomes on current treatments.

A similar number of patients were previously exposed to ADA 203 (30%); 95 (46%) of them reached only 12 months persistence on treatment. Fifty-five (27%) patients stayed on adalimumab over 36 months, with a median treatment duration of 14 months.

A smaller number of patients were exposed to more recently emerged therapies: 20% (135) to VEDO, 54 (8%) to USTEK and only 22 (3%) to TOFA with a median duration of treatment prior to discontinuation of 9 months for VEDO and 7 months for USTEK and TOFA, respectively.

Adverse Events

Overall, an adverse reaction was reported for 67 (10.4%) patients. Frequency of each recorded adverse reaction is listed in Table V. No deaths related to treatment were reported during the study period. Opportunistic infection included in the majority of cases tuberculosis (17/22), followed by varicella zoster virus reactivation (2/22), *Clostridioides difficile* infection (2/22) and one case of cytomegalovirus infection. Five out of the 17 patients with active tuberculosis had disseminated disease and required hospitalization. One of these patients developed life-threatening acute respiratory failure that required intensive care. Inflammatory bowel disease related surgery was documented for 6 CD and 5 UC patients. During the induction period with IFX. 4 patients developed a severe allergic reaction (3 cases of anaphylactic reaction and one case of angioedema).

Treatment was discontinued in 21 (31%) of patients. Type of treatment did not significantly influence the rate of adverse events (p=0.23).

Table V. Frequency of adverse reactions

Adverse reaction	Number of patients (%)
Serious infection	7 (1%)
Opportunistic infection	22 (3.2%)
Hospitalization	5 (0.7%)
Life-threatening event	1 (0.1%)
Worsening of inflammatory bowel disease	9 (1.3%)
Worsening of or extraintestinal manifestations	7 (1.3%)
Cancer	1 (0.1%)
Surgery	11 (1.6%)
Severe allergic reaction	4 (0.6%)

DISCUSSION

For many years, anti-TNF agents were the only available biologic treatment options for IBD patients. With the approval of VEDO, USTEK and TOFA possibilities for targeting and obtaining long-term disease control increased considerably. However, recommendations and strategies for clinical use of these therapies are yet to be established. Current guidelines recommend any of the available molecules (IFX, ADA, TOFA, USTEK, VEDO) for patients with UC that failed conventional therapy [11]. The results of the VARSITY study [12] were incorporated in the latest recommendations, with the suggestion to use VEDO rather than adalimumab for the induction and maintenance of remission in patients with moderate-severe UC [13]. For CD patients that failed conventional therapy, anti-TNF agents are the next recommended option. However, for patients experienced to anti-TNF agents, experts equally suggest the use of either USTEK or VEDO for the treatment of moderate-to-severe active CD [14].

Comparative effectiveness studies are needed to improve the therapeutic decisions for IBD patients. There are a very limited number of studies investigating safety and efficacy of new treatments for real-life cohorts of IBD patients. To the extent of our knowledge, real-world data from Romania on prescribing of advanced therapies for IBD have not been published so far. Our study gathered data from 24 IBD centers nationwide and focused on patients started on advanced therapies during a 24-month period frame (December 2019-December 2022).

Our study offers a narrow perspective on trends in prescribing advanced therapies for IBD patients in a limited period frame. One of the first aspects that needs to be addressed when discussing our results is the patient population. Our cohort included patients usually considered "difficult" or with a "poor prognosis" by current guidelines, needing immunosuppressive and biologic treatments. Considering only 38% of patients included in our study were biologic-naïve with a majority failing at least one line of advanced therapy (61%) and 17% undergoing previous surgery for IBD, results cannot be applied to patients with a more indolent course of disease. Consequently, treatment outcomes and rates of discontinuation could be more optimistic in a more heterogeneous population of IBD patients.

At the present, any of the available advanced therapies can be used as a first-line option for inducing and maintaining remission in IBD patients that failed conventional therapies [13, 14]. However, for patients failing a first line of biologic therapy, there is insufficient data on comparative efficacy or safety, therapeutic decisions are tailored to each patient [14-17]. Our results show that in biologic-naïve patients, physicians prefer anti-TNF patients as first line of treatment (72% of cases). This data is consistent with recent findings, as an European study shows that physicians largely preferred IFX and ADA or their biosimilars as first-line therapy both in UC and CD [18]. Overall, during December 2019- December 2021 in Romania, the most frequently prescribed treatment was VEDO. When analyzing these results, we must consider that 44% of patients had already failed an anti-TNF agent and TOFA and USTEK became available in our country later on.

Positioning the use of different medical therapies and setting treatment targets are redefined as more data becomes available [19-21]. Standardized and validated measures for treatment outcomes (e.g. clinical remission, mucosal healing) are not widely used in clinical practice and are often modified in a rapidly evolving medical field [2]. Persistence of patients on different therapies has emerged as an indirect measure of treatment efficacy and safety and could help establish therapeutic strategies in the future. Studies investigating this parameter so far, defined long-term persistence on a drug as continuation of treatment over 12 months and early discontinuation as drug withdrawal before 6 months.

Our results show that for patients started on a new treatment in the 24-months study period, only 30-54% of patients reached the 12 months milestone for treatment persistence. For anti-TNF agents, results of our analysis are consistent with previously published data [5, 6]. A possible explanation for lower percentages in case of VEDO, USTEK and TOFA could be the novelty of some of these treatments in Romania.

However, analyzing patterns of discontinuation for advanced therapies, the persistence profiles of advanced therapies show high rates of discontinuation for all molecules. For anti-TNF agents, rates of discontinuation at 12 months of follow-up reached up to 65% in ADA and 54% in IFX treated patients, respectively. Previous studies showed that 10-40% of patients treated with anti-TNF agents experience primary nonresponse [22] and up to 50% of patients develop secondary loss of response in the first 12 months of therapy [23]. For newer therapies, previous exposure was recorded in a small number of patients and were discontinued after shorter periods of time (after only 7 months for TOFA and USTEK). A possible explanation could be previous exposure to advanced therapies, a known predictor of non-response to a second/third line of treatment.

Limited data available so far suggest that long-term persistence of biologics is low, results that are confirmed by our analysis. With the longer history of prescribing anti-TNF agents, most data is available for these molecules. Only 19% of IFX and 27% of ADA treated patients continued treatment after 36 months of follow-up. In another 20-year real-world study, including 538 patients, nearly half of patients withdrew from treatment within 2 years [24].

The main reason for treatment discontinuation for anti-TNF agents was loss of response (58% for IFX and 63% for ADA, from the total number of discontinued patients), followed by lack of initial response. Secondary loss of response was more frequent in our study population compared to data published so far. For example, data from the ACCENT1 trial (including more than 6,000 patient-years of follow-up) estimates that approximatively 40% of patients with CD treated with IFX will lose response eventually, and the annual risk for loss of response to IFX is about 13% per patient-year of treatment [25]. Therapeutic drug monitoring is wide available in Romania and could explain these results by early detection of inadequate drug trough levels or anti-drug antibodies. In case of VEDO, the proportion of patients that lacked an initial response was similar with the loss of response rate (48%) and data reported so far. For example, results of a meta-analysis conducted by Peyrin-Biroulet et al. [26] showed a pooled incidence rates of loss of response of 47.9 per 100 person-years of follow up (95% CI, 26.3–87.0; I2=74%) among patients with CD and 39.8 per 100 person-years of follow up (95% CI, 35.0–45.3; I^2=0%) among patients with UC. An adverse event was the cause of discontinuation more frequently for anti-TNF agents, results that are easily explained by the drugs mechanism of action and safety profiles.

In our mixed cohort (biologic-naïve and experienced patients) rates of clinical remission ranged from 61-77% and 21-43% reached mucosal healing. Considering data was collected retrospectively and patients were followed by different protocols, a comparative analysis between molecules was not possible. These results however indicate that with available therapies treatment targets are reached and maintained for an insufficient number of patients.

Future studies could compare corresponding data for other countries to see how differences in healthcare systems and management strategies affect patterns of use of biologics in IBD. Given the high rates of discontinuation for biologics resulted from available research, our study included, clinicians should base their decision to stop an advanced therapy on solid clinical and/or endoscopic data after adequate optimization of treatment. Considering therapeutic alternatives, clinicians may be prone to deciding on a premature switch of therapy. Clear and consistent recommendations are needed to guide treatment strategies and fully utilize available resources [27].

Our results show that patients with CD have a higher chance to continue treatment at 6 and 12 months of follow-up, data supported by previous studies. A Korean nationwide population-based study investigating anti-TNF treated patients showed similar rates of discontinuation at one year of treatment, with higher rates of non-persistence in UC patients [28]. Disease duration has been investigated as a potential predictor for response to anti-TNF therapies and patients with shorter disease duration have a better response to early treatment [29].

In our analysis, we recorded an adverse event for 10.4% of patients, with a severe adverse event <1%. Considering the retrospective design of our study, the low adverse event rate can be attributed to underreporting and missing data. Large-scale cohort studies however support the safety of these drugs [3, 4].

CONCLUSIONS

Biologic-experienced IBD population in Romania is increasing and is becoming more and difficult to obtain long-term disease control. In this difficult to treat IBD population, discontinuation rates for advanced therapies are high. Although significant safety concerns do exist with the use of advanced therapies, severe adverse events rarely occur and data from our study and other large cohort-studies are generally reassuring.

Conflicts of interest: None to declare.

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Authors' contributions: R.B.M. designed the study. M.S., T.V. analyzed the data and drafted the manuscript. All authors discussed the results and contributed to the final version of the manuscript. L.N. critically revised the manuscript. All the authors approved the final version of the manuscript.

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