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ORIGINAL RESEARCH

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Second-line strategies after anti-TNF failure in chronically active, moderate-to-severe ulcerative colitis: a retrospective, multicentre cohort study

Bernadett Farkas [a], Jimmy K. Limdi[b], Péter Bacsur [a], Edoardo Vincenzo Savarino[c,d], Luisa Bertin[c,d], Karishma Sethi-Arora[b], Pál Miheller[e], Fruzsina Vilmos[e], Fabiana Castiglione[f], Livio Bonacci[f], Milan Lukas[g], Nitsan Maharshak[h,i], Galia Berman[h,i], Željko Krznaric[j,k], Panu Wetwittayakhlang[l,m], Peter L. Lakatos[l,n], Jakob Benedict Seidelin[o], Mohamed Attauabi[o], George Michalopoulos[p], Davide Giuseppe Ribaldone[q], Anna Kagramanova[r,s], Elena Chashkova[t,u], Patrícia Sarlós[v,w], Simone Saibeni [x], Ariella Bar-Gil Shitrit[y], Mariann Borsos[z], Tamás Resál[a], Zoltán Szepes[a], Tamás Molnár[a] and Klaudia Farkas[a,aa]

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ABSTRACT

Background: Many ulcerative colitis (UC) patients require the use of second-line agents after the failure of anti-TNF therapy.

Research design and methods: We conducted a multicenter, retrospective study including 683 chronically active, moderate-to-severe UC patients who failed first-line anti-TNFs. The rate of treatment persistence and colectomy-free survival was assessed up to 3 years after the initiation of second-line therapy. Predictors for colectomy and persistence were investigated.

Results: After the failure of the first-line anti-TNF, ustekinumab had superior persistence and colectomy-free survival rates compared to tofacitinib ($p = 0.05$; $p = 0.001$) and vedolizumab ($p = 0.02$; $p = 0.05$), but significant difference was only found in persistence rates in comparison with anti-TNFs ($p < 0.001$). Regardless of the number of prior anti-TNFs, significantly higher persistence ($p = 0.05$) and colectomy-free survival rates ($p = 0.01$) were observed over 2 years with ustekinumab than with vedolizumab or tofacitinib, whereas ustekinumab's superiority over tofacitinib seemed to disappear by the third year. Hypoalbuminaemia ($p = 0.002$) and shorter disease duration at second-line initiation ($p = 0.03$) increased, while concomitant immunomodulators ($p = 0.05$) reduced the risk for colectomy. Shorter disease duration ($p = 0.01$) and primary non-response to the previously used anti-TNF ($p < 0.001$) negatively influenced persistence with second-line non-TNF-targeted agents.

Conclusion: After first-line anti-TNF failure, switching to a non-anti-TNF agent is worth considering in moderate-to-severe UC.

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KEYWORDS
anti-TNF failure; biological therapy; sequential therapy; ulcerative colitis; inflammatory bowel diseases

1. Introduction

The introduction of anti-TNF agents has brought major advances in the treatment of inflammatory bowel disease (IBD). Yet, a significant proportion of patients do not respond favorably to first-line biological therapy, which may require the use of second-, third-, or even fourth-line agents. Treatment selection and sequencing, however, remain a major unresolved issue. While studies suggest that in biologic-naive, moderate-to-

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severe ulcerative colitis (UC) patients the use of infliximab (IFX), vedolizumab (VDZ) and ustekinumab (UST) appeared to be the most beneficial, in bio-experienced UC patients UST, and small-molecule agents (e.g. tofacitinib [TOFA]) are the most effective at inducing remission [1–3]. Notwithstanding indirect evidence from network-analyses, the number of real-world studies investigating the effectiveness of second-line therapeutic options after anti-TNF failure is still limited [2,4–9]. Treatment persistence is a composite measure of real-world effectiveness, safety, tolerability, and general patient satisfaction with biological and small-molecule therapy [10]. Therefore, examining treatment persistence and colectomy-free survival in anti-TNF refractory UC patients may provide valuable data on the long-term applicability of sequential therapy, and non-TNF-targeted biologics.

Despite the growing therapeutic arsenal, the 5- and 10-year risk of colectomy in UC patients still remains at 10%–15%, which may increase up to 40% in a subset of patients with complicated, refractory disease [11]. According to the currently available data, sequential therapy may reduce the need for colectomy in the short term, but data on the long-term outcome of this treatment strategy are limited [12]. Furthermore, considering that the effectiveness of most biological therapies appears to be lower after anti-TNF treatment, the identification of an effective, second-line non-anti-TNF agent may have crucial importance in daily practice [13].

To address this unmet need, we conducted a multicenter, retrospective, real-world study, which aimed to evaluate the effectiveness of sequential biological and small-molecule therapies, especially second-line agents, by comparing the rates of treatment persistence and colectomy-free survival in anti-TNF refractory UC patients.

2. Patients and methods

2.1. Study design and settings

Data were collected from 26 tertiary centers in Europe, Israel, and Canada from January 2003 to June 2023. The required data were retrieved from local medical record systems and entered into a purpose-designed, unified database by all investigators. The follow-up time was estimated from the initiation of the first-line anti-TNF therapy to the last UC-related medical visit in the study period and was essentially equivalent to cumulative duration of biologic and small-molecule exposure across first-, second-, or even third- and fourth-line therapies. Ethical approval for the study was obtained from the Regional and Institutional Human Medical Biological Research Ethics Committee, University of Szeged on 22 May 2022 (76/2023-SZTE RKEB). The research was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). Patient consent was waived by the Ethics Committee due to the retrospective nature of the study.

2.2. Participants

Only diagnosed UC patients (based on clinical, biochemical, endoscopic, and histological findings) (1) with ≥18 years of age, (2) who received at least one anti-TNF agent (IFX, adalimumab [ADA], or golimumab [GOL]), (3) who were treated with for second-, third-, and fourth-line biologics or small molecules for chronically active, moderate-to-severe UC (CA; as defined by pMayo scores ≥5 [14]) were included in the study. We enrolled patients who had up to three lines of anti-TNFs before switching out of class, and each was considered to be a new line of therapy. Participants (1) with acute severe UC (based on the Truelove-Witts criteria [15]) at the initiation of second-, third-, and fourth-line agent, (2) who received a non-anti-TNF drug as first-line therapy, and (3) who underwent colectomy prior to second-line therapy were excluded. The disease phenotype was defined according to the Montreal classification [16]. Clinical and endoscopic disease activity was evaluated using the partial Mayo score (pMayo) and the Mayo endoscopic subscore (eMayo) [17].

2.3. Data collection

The demographic data and clinical characteristics included date of birth, sex, smoking habit, date of UC diagnosis, disease extent, and severity at diagnosis and during follow-up. The presence of deep ulcers was reported based on a unified definition of a profound loss of tissue compared with the surrounding edematous mucosa at the time of diagnosis and during the follow-up period [18]. The type and duration of therapy, and the reason for treatment discontinuation were recorded. If the exact day of the treatment initiation or discontinuation was not provided, the first day of the indicated month was entered into the database. Serum albumin levels were assessed at the time of treatment initiation (within one week). The use of concomitant immunomodulators (IMM; azathioprine, 6-mercaptopurine) was also noted, along with the need for dose intensification. Furthermore, the date and indication of colectomy were also reported.

2.4. Outcomes

The co-primary endpoints were to determine the rate of colectomy-free survival and treatment persistence up to at least 3 years post-initiation of sequential therapy. Colectomy-free survival was defined as not undergoing colectomy during the administration of the biologic or small-molecule agent. Treatment persistence was defined as the proportion of patients who had not discontinued biologics or small molecules at the time of inquiry. The secondary outcome was the identification of the most effective second-line therapy in UC based on persistence and colectomy-free survival rate. Second-line therapy was investigated in two different settings, initially after the discontinuation of the first-line anti-TNF agent, and finally after failure of one or more anti-TNFs, following the initiation of the first non-anti-TNF biologic or small molecule. Other endpoints were the detection of factors, which may predict colectomy and persistence with non-anti-TNF agents, as well as the assessment of the effectiveness of third-line therapies following the failure of anti-TNF and second-line non-anti-TNF treatment.

2.5. Statistical methods

All statistical analysis was carried out using the program SPSS (IBM Statistical Package for Social Sciencies for Windows,

version 29.0, IBM Corp., Armonk, NY). Descriptive statistical analysis was presented as median with interquartile range (IQR) or mean with standard deviation (SD) for continuous variables. Categorical variables were summarized using frequency and percentage. Differences in continuous variables were assessed using independent samples t-tests, and repeated measures analysis of variance (ANOVA). The chi-square test was used to determine the associations between patient groups and categorical variables. The incidence of dose escalation was presented using descriptive statistical methods, namely by the percentage of patients who required a dose adjustment to achieve adequate treatment effectiveness. Kaplan–Meier analyses were performed to assess the rates of colectomy-free survival and treatment persistence. Colectomy-free survival rates were estimated by including patients who had the exact date of the initiation of the second-, third-, and fourth-line therapeutic agent, and the colectomy, the date of treatment discontinuation, or the last medical checkup. Patients who did not have a colectomy or did not discontinue the biological or small-molecule agent during the assessed time period were censored in the survival analysis. Various biological and small-molecule agents were compared by logrank test during the evaluation of outcomes. A multivariate Cox regression model was used to investigate the factors associated with colectomy and persistence. First, we developed a model using clinically relevant factors and then used backward elimination to identify the variables remaining in the model (using a limit of $p \leq 0.15$). A p-value less than 0.05 was considered significant. Incomplete or missing data were not imputed.

3. Results

3.1. Baseline characteristics

A total of 683 UC patients (mean age: 43.7 ± 14.6 years; male/female ratio: 361/322) were enrolled in the study. The median follow-up time was 63.5 months (IQR: 99.5–37.3). Patient demographics and disease characteristics are shown in Table 1. Flowchart for the enrollment and follow-up of participants are presented as Supplementary Material (Figure S1). None of the patients included in the present study underwent a planned drug holiday during the follow-up period.

3.2. Treatment characteristics

The mean time elapsed between UC diagnosis and the initiation of first-line anti-TNF therapy was 6.9 ± 7.5 years. Treatment patterns across the lines of sequential therapy are shown in Figure 1.

The median time of treatment persistence with first- (n = 683), second- (n = 683), third- (n = 439), or fourth-line (n = 186) biologics and small molecules were 10.1, 14.8, 21.4, and 48.0 months, respectively. Persistence rates rose significantly as the number of lines of therapy increased ($p < 0.001$; Figure 2(a)). Dose escalation became less frequent with

Table 1. Baseline demographic and clinical data of the cohort study.

Baseline characteristics (n = 683)	
Male (n;%)	361 (52.8%)
Age (years; mean ± SD)	43.7 ± 14.6
Patients' place of origin (n;%)	
Europe	586 (85.8%)
Canada	39 (5.7%)
Israel	58 (8.5%)
Age at the diagnosis (years; mean ± SD)	30.7 ± 13.6
Disease duration (years; mean ± SD)	12.9 ± 8.3
Follow-up time (months; median [IQR]; mean± SD)	63.5 [37.3–99.5]; 75.9 ± 89.6
Extent of the disease (at diagnosis) (n;%)*	
E1 - Proctitis	80 (12.0%)
E2 - Left sided colitis	214 (32.1%)
E3 - Pancolitis	373 (55.9%)
Endoscopic Mayo score at diagnosis (n;%)	
eMayo 1	22 (4.7%)
eMayo 2	253 (53.7%)
eMayo 3	196 (41.6%)
Presence of deep ulcers at diagnosis (n;%)	
No deep ulcerations	337 (49.3%)
Deep ulcers	131 (19.2%)
No data on endoscopy or the presence of ulcers	215 (31.5%)
Partial Mayo score at diagnosis (median, [IQR])	6 [5-7]
Smoking habit	
Never smoked	412 (60.4%)
Former smoker – quit before the diagnosis	99 (14.5%)
Active smoker or quit after the diagnosis	105 (15.4%)
No data	66 (9.7%)
Indication of first-line anti-TNF therapy (n;%)	
ASUC	194 (28.4%)
CA	489 (71.6%)

Ab breviations: ASUC= acute severe ulcerative colitis; CA= chronic active ulcerative colitis; eMayo= endoscopic Mayo subscore; IQR= interquartile range; n= number of patients; SD= standard deviation; TNF= tumor necrosis factor.
*Montreal classification.

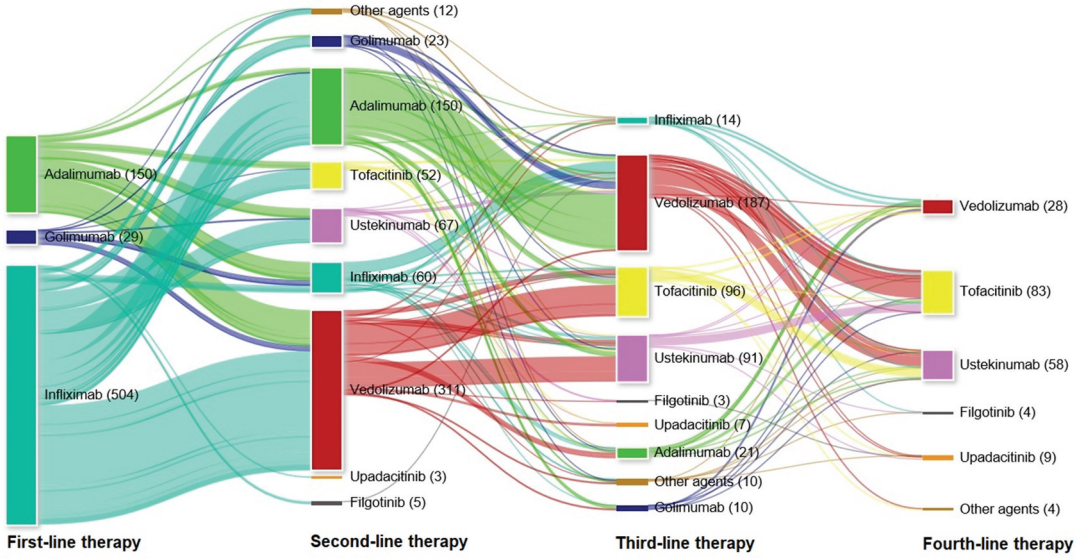

Figure 1. Sankey diagram of treatments received. 683 patients received second-line treatment, while 439 (71.6%) patients started third-line and 186 (27.2%) patients received fourth-line sequential therapy.

Other agents: anrukinzumab, mirikizumab, UTTR1147A, ertolizumab, tacrolimus, ozanimod, AMG181, efavaleukin-alfa, risankizumab, PRA023, guselkumab.

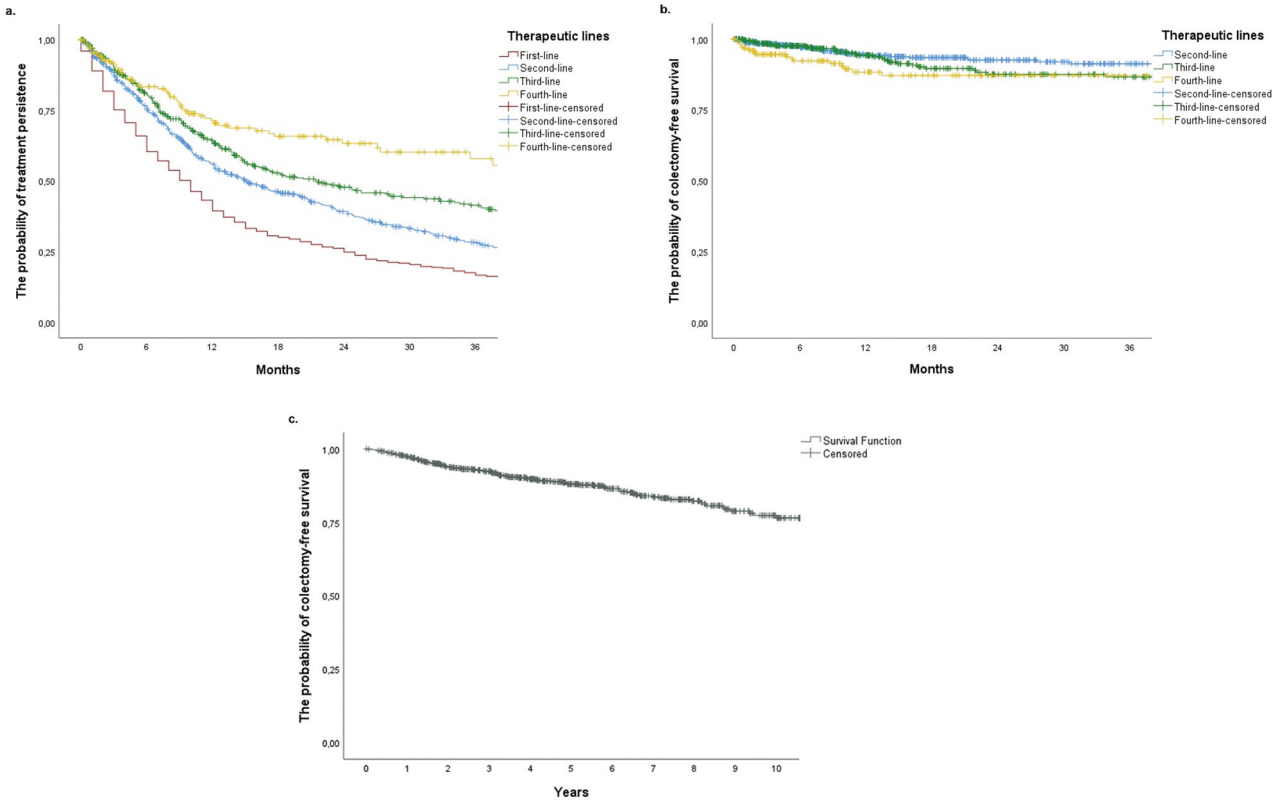

Figure 2. (a) The 3-year treatment persistence rates (based on Kaplan–Meier survival analysis) among patients treated with first-, second-, third-, or fourth-line biological and small molecule therapy. (b) The 3-year colectomy-free survival rates (based on Kaplan–Meier survival analysis) among patients treated with second-, third-, or fourth-line biological and small molecule therapy. (c) The cumulative probability of colectomy-free survival in patients with moderate-to-severe UC (up to 10 years).

sequential therapy (first-/second-/third-/fourth-line: 42.1%/40.0%/36.4%/29.7%; $p = 0.04$).

The overall colectomy rate was 14.2% ($n = 97$; mean disease duration at the time: 8.5 (±7.5) years) during the follow-up period. The probability of colectomy-free survival was 97.5%, 93.9%, 92.3%, 87.9%, and 76.5% at 1, 2, 3, 5, and 10 years, respectively (Figure 2(b)). In 64.9% of the patients, the indication of colectomy was CA, in 23.7% ASUC, and in 11.4% other

causes, such as perforation ($n = 3$), intraabdominal abscess ($n = 2$), and colorectal cancer ($n = 6$).

3.3. The effectiveness of second-line agents after the failure of the first-line anti-TNF agent

The most commonly used agents after the failure of first-line anti-TNF and the clinical characteristics observed at treatment initiation are presented as Supplementary Material (Table S1). After the failure of the first-line anti-TNF agent, 41.2% ($n = 40$) of the patients from Israel and Canada were switched to second-line anti-TNF treatment, whereas 58.8% ($n = 57$) of the patients were switched out of class (e.g. n-[VDZ] = 47; n[UST] = 4; n[TOFA] = 5). In patients from Europe, 32.9% ($n = 193$) received second-line anti-TNFs, while 67.1% ($n = 393$) were treated with non-TNF targeted therapies (e.g. n[VDZ] = 264; n[UST] = 63; n[TOFA] = 47). No statistically significant difference in persistence and colectomy-free survival rates was found among second-line anti-TNFs (Supplementary Material; Figure S2); therefore, they were treated as one agent to simplify the comparison with non-anti-TNF targeted agents.

3.3.1. Treatment persistence

Second-line UST ($n = 67$) showed superior at 12 months (80.1% vs. 44.2% vs. 61.8% vs. 43.5%), 24 months (60.7% vs. 23.5% vs. 46.5% vs. 38.0%), and 36 months (54.7% vs. 12.6% vs. 37.8% vs. 38.0%) to anti-TNFs ($n = 233$; $p < 0.001$), VDZ ($n = 311$; $p =$ or TOFA ($n = 52$; $p = 0.05$; Figure 3(a)). The indication for first-line anti-TNF therapy did not have an impact the results obtained ($p = 0.76$)

In cases of loss of response (LOR) to first-line anti-TNF, second-line UST ($n = 37$; 64.9%) also showed the highest persistence rates, respectively, at year 3 after initiation compared to anti-TNFs ($n = 109$; 11.3%; $p < 0.001$), VDZ ($n = 160$; 39.1%; $p = 0.02$) and TOFA ($n = 30$; 47.6%; $p = 0.05$). (Figure 3(b))

3.3.2. Colectomy-free survival

Regarding colectomy-free survival, UST also showed higher survival rates, respectively, compared to VDZ ($p = 0.05$) and TOFA ($p = 0.001$) at the first (100.0% vs. %. vs. 80.4%), second (100.0% vs. 90% vs. 80.4%), and third (100.0% vs. 87.9% vs. 80.4%) year, however no significant difference was observed between anti-TNFs and UST over 3 years (96.8% vs. 100.0%; $p = 0.23$; Figure 3(c)). The indication for first-line anti-TNF treatment did not affect the outcome ($p = 0.57$).

After LOR to the first-line anti-TNF, colectomy-free survival rates did not differ significantly between second-line UST (100.0%), anti-TNF agents (99.0%; $p = 0.57$), and VDZ (87.1%; $p = 0.08$ at year 3), but lower survival rates were observed, respectively, with TOFA treatment (81.1%; $p = 0.03$; Figure 3(d)).

3.4. The effectiveness of second-line non-TNF targeted agents after one or more anti-TNF failure

After the initiation of the second-line non-anti-TNF agent, patients were followed up for a median of 32 months (mean:

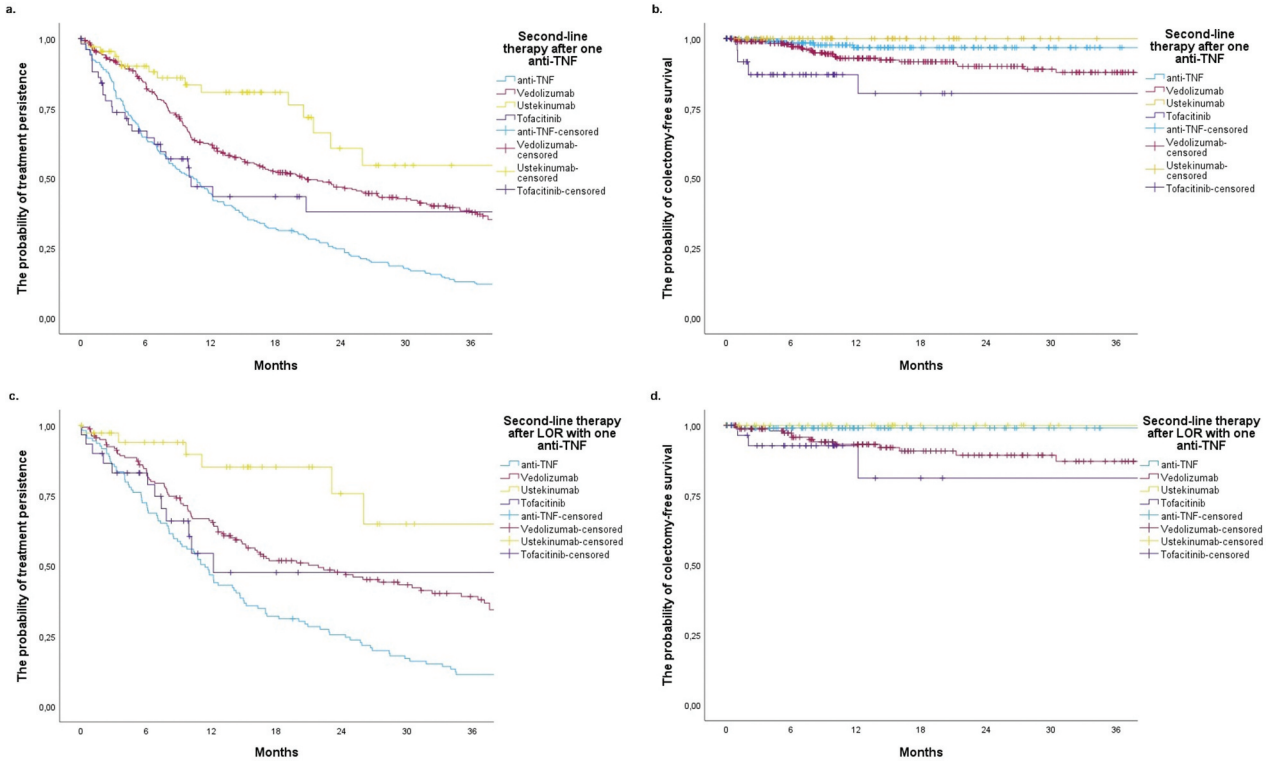

Figure 3. (a) The probability of treatment persistence over 36 months with the most frequently used second-line agents after the failure of first-line anti-TNF therapy. (b) The probability of colectomy-free survival over 3 years with the most frequently used second-line agents after the failure of first-line anti-TNF therapy. (c) Treatment persistence rates over 36 months with the most frequently used second-line agents after loss of response to the first-line anti-TNF therapy. (d) Colectomy-free survival rates over 3 years with the most frequently used second-line agents after loss of response to first-line anti-TNF therapy. Abbreviations: LOR = loss of response; TNF = tumor necrosis factor.

36.2 ± 57.7 months). The baseline and clinical characteristics of the patients treated with the most frequently administered second-line non-TNF targeted therapies (UST, TOFA, and VDZ) are presented in Table 2.

3.4.1. Treatment persistence

The median time of persistence after an anti-TNF failure with second-line UST ($n = 94$), VDZ ($n = 492$), or TOFA ($n = 71$) was 29.3, 23.3 and 37.2 months, respectively.

UST showed superior persistence compared to VDZ and TOFA at 12 months (83.0% vs. 66.5% vs. 59.5%), and 24 months (59.6% vs. 49.8% vs. 51.7%), while at 36 months, a higher rate of persistence was seen with TOFA than with UST or VDZ (51.7% vs. 48.3% vs. 43.3%). (Figure 4(a) ; $p = 0.05$).

A predictive model for persistence was created based on the 12-month follow-up period ($n = 625$), available as Supplementary Material (Table S2.). PNR to the prior anti-TNF (HR: 1.76; 95% CI: 1.26,2,47; $p < 0.001$) and shorter disease duration (HR: 0.97; 95% CI: 0.94,0.99; $p = 0.01$) had a statistically significant negative effect on persistence (Table 3).

3.4.2. Colectomy-free survival

In terms of colectomy-free survival in the first (100% vs. 93.8% vs. 89.0%), second (100% vs. 88.00% vs. 87.5%), and third year

Table 2. The baseline and clinical characteristics of the patients treated with the most frequently administered second-line non-TNF targeted therapies, after one or more lines of anti-TNF failure.

	Vedolizumab (n = 492)	Ustekinumab (n = 94)	Tofacitinib (n = 71)	p-value (VDZ vs. UST vs. TOFA)
Male (n;%)	266 (54.1%)	45 (47.9%)	40 (56.3%)	0.48
Age at the diagnosis (years; mean ± SD)	31.0 (±15.2)	32.0 (±14.0)	30.0 (±10.7)	0.85
Disease duration (years; mean ± SD)	6.6 (±7.4)	9.7 (±7.8)	8.8 (±9.9)	0.76
Follow-up time after second-line treatment initiation (months; median; IQR)		33.9 (50–14)		
Extent of the disease* (n;%)				
E1 - Proctitis	52 (10.9%)	14 (15.1%)	10 (14.1%)	**0.05**
E2 - Left sided colitis	155 (32.5%)	34 (36.6%)	18 (25.3%)	0.31
E3 - Pancolitis	270 (56.6%)	45 (48.4%)	43 (60.6%)	0.49
Presence of deep ulcers (n;%)	94 (19.1%)	19 (20.1%)	16 (22.5%)	0.51
Indication of first-line anti-TNF therapy (n;%)				
ASUC	138 (28.0%)	23 (24.5%)	26 (36.6%)	0.22
CA	354 (72.0%)	71 (75.5%)	45 (63.4%)	
The number of prior anti-TNFs (n;%)				
1 line of anti-TNF	311 (63.2%)	67 (71.3%)	52 (73.2%)	0.15
2 lines of anti-TNF	166 (33.7%)	21 (22.3%)	18 (25.4%)	
3 lines of anti-TNF	15 (3.1%)	6 (6.4%)	1 (1.4%)	
PNR as a reason for discontinuation of the prior anti-TNF (n;%)	142 (28.9%)	23 (24.5%)	20 (28.2%)	0.75
The value of pMayo at second-line therapy initiation ($n = 634$; points; mean ± SD)	6.0 (±2.2)	6.0 (±1.9)	6.0 (±1.7)	0.53
Serum albumin level at second-line therapy initiation ($n = 591$; g/L, mean ± SD)	40.5 (±19.8)	38.0 (±4.6)	38.0 (±5.7)	0.32
Concomitant immunomodulator use (n;%)	126 (25.6%)	18 (19.1%)	12 (16.9%)	0.12
Need for dose intensification (n;%)	198 (40.2%)	25 (26.9%)	24 (34.3%)	**0.02**

Abbreviations: ASUC = acute severe ulcerative colitis; CA = chronic active ulcerative colitis; eMayo = endoscopic Mayo subscore; n = number of patients; PNR = primary non-response; SD = standard deviation, TNF = tumor necrosis factor.
*Montreal classification.

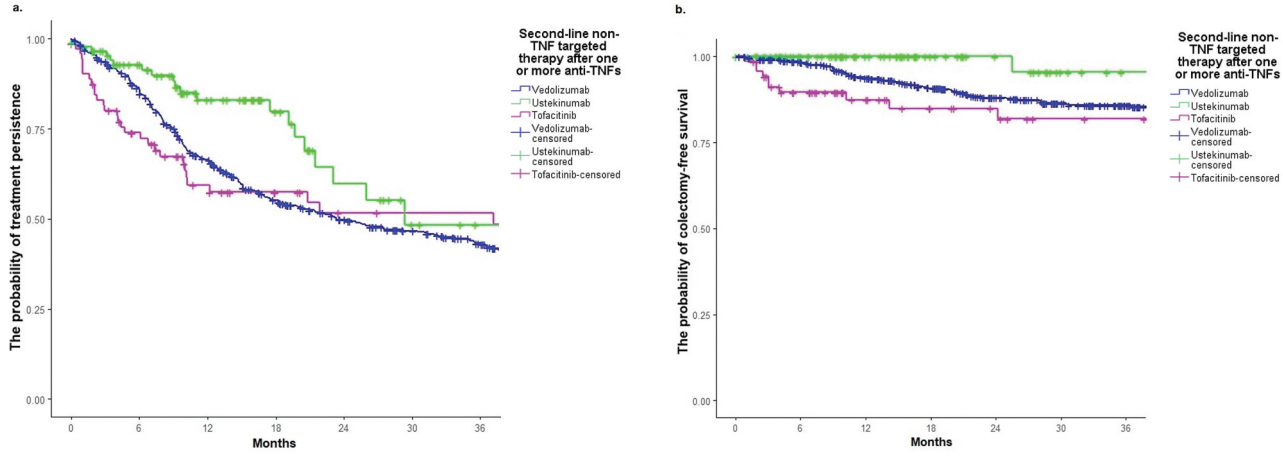

Figure 4. (a) 3-years colectomy-free survival stratified by second-line non-TNF targeted biologics or small molecules, after one or more anti-TNFs. (b) Treatment persistence in patients treated with second-line non-TNF targeted biological or small molecule therapy, after one or more anti-TNFs.

Table 3. Factors influencing colectomy-free survival and treatment persistence with second-line non-anti-TNF agents, based on multivariate cox regression analysis.

Colectomy					Treatment persistence				
Factors	HR	95% CI		*p*-value	*Factors*	HR	95% CI		*p*-value
Serum albumin at second-line treatment initiation	0.87	0.80	0.95	0.002	*Disease duration at second-line treatment initiation*	0.97	0.95	0.99	0.01
Concomitant immunomodulator use	0.27	0.07	1.01	0.05	*PNR as the reason for discontinuation of the prior anti-TNF*	1.77	1.26	2.47	<0.001
Disease duration at second-line treatment initiation	0.91	0.19	1.94	0.03					

Ab breviations: CI = confidence interval; HR = hazard ratio; *n* = number of patients; PNR = primary non-response; TNF = tumor necrosis factor; TOFA = tofacitinib; UST = ustekinumab; VDZ = vedolizumab.

(95.5% vs. 85.8% vs. 85.6%), UST was shown to be superior to VDZ and TOFA ($p = 0.01$) (Figure 4(b)).

Various demographic and clinical data, as well as laboratory parameters were analyzed to predict colectomy with second-line non-TNF targeted agents after anti-TNF failure, presented as Supplementary Material (Table S3.). According to the final regression model, low serum albumin level (HR: 0.87; 95% CI: 0.80,0.95; $p = 0.002$) and shorter disease duration (HR: 0.91; 95% CI: 0.19,1.94; $p = 0.03$) at treatment initiation increase, while concomitant IMMs (HR: 0.27; 95% CI: 0.07,1.00; $p = 0.05$) reduce the risk of colectomy (Table 3).

3.5. Effectiveness of non-TNF targeted agents initiated in 2019–2023 following the failure of one or more anti-TNF agents

In order to assess whether the availability of treatment options might influence the outcomes, we performed a sub-analysis including patients who received second-line VDZ, UST, and TOFA between 2019 and 2023, after failure of one or more lines of anti-TNF therapy.

Second-line UST ($n = 88$) showed superior persistence at 12 months (80.5% vs. 57.6% vs. 53.7%), 24 months (63.7% vs. 41.0% vs. 46.6%), to both VDZ ($n = 248$; $p < 0.001$) and TOFA ($n = 59$; $p = 0.05$), whereas UST's superiority over TOFA seemed to disappear by month 36 ($p = 0.51$), while against VDZ it remained evident (49.3% vs. 35.7% vs. 46.6%; Figure S3).

Second-line UST also showed higher colectomy-free survival rates at 12 months (100% vs. 86.5%), 24 months (92.3% vs. 80.3%), and 36 months (92.3% vs. 80.3%) to TOFA ($p = 0.007$), whereas in contrast to VDZ ($p = 0.21$) UST did not show significantly better survival rates at month 12 (100% vs. 95.9%), at 24 months (92.3% vs. 91.9%) and 36 months (92.3% vs. 91.9%). (Figure S4).

3.6. The effectiveness of third-line ustekinumab and tofacitinib after anti-TNF and vedolizumab failure

After the failure of the second-line VDZ therapy ($n = 165$), 73 patients were started on UST, while 81 patients were treated with TOFA. There was no statistically significant difference in the probability of treatment persistence at 12 months between the third-line UST (54.4%) and TOFA (53.1%; $p = 0.81$; Figure S5). A statistically significant difference was seen in 12-month colectomy-free survival between the third-line UST (98.3%) and TOFA (82.6%; $p = 0.03$; Figure S6). However, it should be highlighted that patients receiving third-line TOFA had significantly higher baseline pMayo points than those receiving third-line UST (Table S4). This may indicate that the poorer colectomy-free survival rates with TOFA may be due to the fact that patients in this group had more severe disease.

4. Discussion

In this retrospective, multicenter, observational study, we provide real-world data demonstrating the probability of colectomy-free survival and treatment persistence in moderate-to-severe UC after multiple lines of sequential therapies. We found that following the discontinuation of first-line anti-TNFs, especially in the case of LOR, the use of second-line non-TNF-targeted agents resulted in higher persistence rates over 3 years post-initiation. There was no evident long-term superiority in terms of persistence and colectomy-free survival between second-line UST, VDZ, and TOFA therapy. After the failure of anti-TNF and second-line VDZ, there was no statistically significant difference between patients receiving third-line UST or TOFA in terms of the 1-year persistence rates.

Whether the introduction of biologics has been associated with a change in the natural course of UC is a matter of debate. According to a recent systematic review and meta-analysis, the relative risk of colectomy has decreased with the introduction of biologics, with prevalence rates of 10.0% in the tenth year after diagnosis [19]. In the present study, we observed a higher need for colectomy by year 10 (23.7%), which might be due to the refractory patient population included in our cohort.

There is a lack of data on treatment persistence among bio-exposed UC patients. The generally higher persistence rates in previous studies compared to the findings of this study are likely due to the mixed (biologic-naive and experienced) patient population [20–22]. In the present study, persistence rates increased significantly with the number of treatment lines. It seems plausible that as the number of therapeutic failure increases, clinicians may synchronously strive to maximize the use of available therapeutic options before sequencing further. However, it is not feasible to investigate the impact of this complex confounder on the results obtained, not only due to the retrospective nature of the study but also because in many European countries, national regulations still determine the time and/or the order of the administration of the various therapeutic options. Noteworthy, a recent study reported relatively high persistence rates with fourth and fifth lines of therapy among difficult-to-treat IBD patients [23].

There are limited studies on the effectiveness of sequential therapy, especially in terms of second-line treatment options [2,5,6,8,9]. While the therapeutic arsenal is growing, real-world, head-to-head trials with the most commonly used biologics and small molecules are lacking.

The data reported by Kapizioni et al. support our findings that following LOR to the first-line anti-TNF therapy, second-line VDZ were associated with superior persistence compared to second-line anti-TNFs [4]. A recent retrospective observational study demonstrated that TOFA is more effective as third-line therapy (after anti-TNF and VDZ failure) in reducing the risk of disease progression, than UST. Yet, no statistically significant differences were seen for clinical remission, normalization of CRP and persistence [24]. Nevertheless, a retrospective cohort study reported similar effectiveness with UST and TOFA at 1 year after anti-TNF failure [7]. Previous studies comparing VDZ and TOFA, or VDZ and UST in moderate-to-severe UC are conflicting, either show no difference between the two agents or consider VDZ to be inferior in clinical outcomes [5,6,8,9]. According to a systemic review and metaanalysis, TOFA and UST were ranked highest in UC patients after anti-TNF exposure [2].

To date, the only study available comparing the effectiveness of the three most frequently used second-line therapies after anti-TNF failure is a recently published American propensity-matched cohort study [25]. Similar to our results, the risk of colectomy in UC was higher with both VDZ (aOR: 1.67) and TOFA (aOR: 2.63) than with UST. Moreover, change in therapy was more frequently required during the 2-year follow-up period with TOFA and VDZ than with UST (TOFA vs. UST: aOR: 2.38; VDZ vs. UST: aOR: 1.45).

The retrospective nature of the study limited our ability to assess whether the poorer outcomes in patients receiving second-line TOFA were due to more severe disease. Notably, we did not see significant differences in disease extent, the presence of deep ulcers, or clinical activity at the time of treatment initiation, between the most frequently administered second-line agents.

It is unclear why the superiority of UST is not sustained in the third year after anti-TNF failure, but we speculate that the shorter follow-up times are the cause of this observation.

Our results suggest that shorter disease duration and PNR to the previously used anti-TNF negatively impacts persistence with second-line non-anti-TNF agents. In a retrospective cohort, shorter disease duration was independently associated with the increased risk of treatment failure in biologic-treated UC, suggesting that the early need for advanced therapies can be a poor prognostic factor [26]. In line with the findings of Singh et al., PNR to the previously administered anti-TNF negatively impacted the effectiveness of second-line agents, which may be due to currently unknown pharmacokinetic or pharmacodynamic mechanisms [13].

We noted a higher risk of colectomy with second-line non-TNF targeted agents with low serum albumin levels and shorter disease duration at treatment initiation, while the risk decreased with concomitant IMM use. Not only does hypoalbuminaemia imply a more severe disease phenotype, but previous studies have shown that serum albumin concentration is inversely related to drug clearance for biologics [27–30]. The literature on the efficacy of concomitant IMMs with non-anti-TNF agents remains conflicting [31–33]. Concomitant IMM use was observed in 12 patients during TOFA treatment. Notably, none of the patients were started on IMM therapy synchronous with TOFA, and in all patients the concomitant IMM was stopped in the first few weeks of the induction phase, without any adverse reaction. Given that there is currently no evidence on the effectiveness and safety of the combined use of JAK inhibitors and IMMs, this treatment strategy is not recommended.

We acknowledge some limitations in our study. The key limitation is its retrospective nature, which introduces confounding through inherent variability with assessments. Furthermore, we did not analyze clinical, biomarker, endoscopic, and histologic outcomes. However, rate of long-term persistence and colectomy-free survival may indirectly indicate the effectiveness and safety of therapies. Selection bias may have occurred as centers were likely to have selected patients who had attended a UC-related medical visit during the data collection period and met the inclusion criteria. The retrospective nature of the study precluded random allocation of treatment groups and also due to a lack of previous studies, calculation of a sample size was not possible. Multivariate Cox regression analyses were applied to assess potential covariates and confounders, instead of propensity score matching. Statistical analyses regarding the second-line therapy did not include recently licensed biologics or small molecules (e.g. upadacitinib), due to the low number of patients affected in this study. Differences in the number of patients receiving second-line VDZ, TOFA, and UST treatment may have influenced the results obtained. Although we did a subanalysis of the time period (2019–2023) for which both VDZ, UST, and TOFA were already licensed for UC treatment, we were not able to investigate the differences in national regulations between the participating centers and their potential impact on the outcomes. We did not collect data on the exact dosage regimens of the different treatments but assessed whether dose escalation was needed during the sequences. No information is available on the results of therapeutic drug monitoring, as well as on the incidence of IBD-related hospitalizations or ASUC episodes. We have not investigated the possible reasons behind LOR to anti-TNFs. Co-administration of corticosteroids at baseline and the need for courses of corticosteroids during the subsequent lines of treatment have also not been reported, as the study design does not allow for an accurate assessment and follow-up of this factor. However, the need for or frequent use of corticosteroids alongside a biologic or small molecule will eventually lead to treatment discontinuation or colectomy, and will most certainly have an impact on the outcomes examined.

Our study has several notable strengths. This is one of the first real-world studies to evaluating the long-term outcome of sequential biological and small-molecule treatment in a large cohort of refractory UC patients. This cohort is also the first to compare second-line anti-TNFs, VDZ, UST, and TOFA therapy, following the failure of first-line anti-TNF. Moreover, we provide real-world data on the long-term success of the most

commonly used non-anti-TNFs after anti-TNF failure. Multivariate Cox regression analyses were applied to assess potential covariates and confounders.

5. Conclusions

Even after multiple lines of sequential biological and small-molecule therapy, we noted a low incidence of colectomy and a high rate of persistence. After the failure of first-line anti-TNF therapy, especially in cases of LOR, switching to a non-anti-TNF agent is worth considering in patients with chronically active, moderate-to-severe UC. No evident long-term superiority was observed between second-line UST, VDZ, and TOFA therapy in terms of treatment persistence and colectomy-free survival rates. However, prospective controlled trials addressing objective clinical, biochemical, and endoscopic parameters are needed to confirm our findings and to further understand the outcomes with biological and small-molecule treatment sequencing.

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Declaration of interest

JK Limdi has been a speaker and/or advisory board member for AbbVie, Arena, BioHit, Bristol Myers Squibb, Eli Lilly, Ferring, Galapagos, Janssen, MSD, Pfizer, Takeda, and Tillots and has received research grants from Galapagos and Takeda. EV Savarino has served as speaker for AbbVie, Agave, AGPharma, Alfasigma, Aurora Pharma, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Fenix Pharma, Fresenius Kabi, Galapagos, Janssen, JB Pharmaceuticals, Innovamedica/Adacyte, Malesci, Mayoly Biohealth, Omega Pharma, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Tillots, and Unifarco; has served as consultant for AbbVie, Agave, Alfasigma, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Dr. Falk, Fenix Pharma, Fresenius Kabi, Janssen, JB Pharmaceuticals, Merck & Co, Nestlè, Reckitt Benckiser, Regeneron, Sanofi, SILA, Sofar, Synformulas GmbH, Takeda, and Unifarco; and has received research support from Pfizer, Reckitt Benckiser, SILA, Sofar, Unifarco, and Zeta Farmaceutici. K Sethi-Arora has received speaker fees from Celltrion, Galapagos, and Takeda. F Castiglione has received speaker's honoraria from Pfizer, AbbVie, Janssen, Galapagos, Alfasigma, Takeda, and Biogen. M Lukas has been a speaker for AbbVie, Takeda, Celltrion, Biogen, and Janssen Cilag. N Maharshak has received speaking and/or consulting fees from Pfizer, AbbVie, Lilly, Takeda, Janssen, Ferring, BiomX, BMS, Nestle, Trobix, Teva, and grant support from Takeda, Janssen, Abbott, AbbVie, Pfizer, BMS, Corundum Innovation Ltd., and Nestle. Ž Krznarić has recived speaker's honoraria from AbbVie, Janssen, Ferring, Takeda, Pfizer, Sandoz, and Fresenius. PL Lakatos has been a speaker and/or advisory board member for AbbVie, Amgen, BioJamp, Bristol Myers Squibb, Fresenius Kabi, Genentech, Gilead, Janssen, Merck, Mylan, Organon, Pendopharm, Pfizer, Roche, Sandoz, Takeda, Tillots, and Viatris, and has received unrestricted research grant: AbbVie, Gilead, Takeda and Pfizer. JB Seidelin has received research grants from Takeda, Janssen, the Danish Research Council, and the Capital Region Denmark, and is national coordinator of studies from AbbVie, Arena Pharmaceuticals, Ely Lilly, and Boehringer Ingelheim. G Michalopoulos has received speaker's honoraria from MSD, Takeda, Janssen, Amgen, and AbbVie. DG Ribaldone declares the following paid consultancies and lecture fees for the past 2 years: AbbVie, Janssen, Takeda, Galapagos, Biogen, and Celltrion. E Chashkova has served as speaker for AbbVie, Janssen, and Takeda. S Saibeni declares the following paid consultancies, lecture fees: AbbVie, Arena, Ferring, Galapagos, Gilead, Janssen, MSD, Pfizer, and Takeda. T Molnár has received speaker's honoraria from MSD, AbbVie, Egis, Goodwill Pharma, Takeda, Pfizer, Janssen, Sandoz, MundiPharma, Phytotec, Roche, Fresenius, Bristol-Myers Squibb, Lilly, and Teva. K Farkas has received speaker's honoraria from AbbVie, Janssen, Ferring, Takeda, Pfizer, Bristol-Myers Squibb, and Goodwill Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Author contributions

B Farkas: Conceptualization, Investigation, Data curation, Methodology, Project Administration, Formal analysis, Visualization, Writing – original draft; JK Limdi: Data curation, Writing – review and editing, Supervision.; P Bacsur: Investigation, Validation, Writing – review and editing; EV Savarino, L Bertin, K Sethi-Arora, P Miheller, F Vilmos, F Castiglione, L Bonacci, M Lukas, N Maharshak, G Berman, Ž Krznarić, P Wetwittayakhlang, PL Lakatos, JB Seidelin, M Attauabi, G Michalopoulos, DG Ribaldone, A Kagramanova, E Chashkova, P Sarlós, S Saibeni, ABG Shitrit, T Resál, Z Szepes: Investigation, Data curation, Writing – review and editing, Supervision; M Borsos: Software, Formal analysis, Visualization, Validation, Writing – review and editing; T Molnár: Conceptualization, Methodology, Resources, Funding acquisition, Supervision, Writing – review and editing; K Farkas: Conceptualization, Investigation, Methodology, Resources, Funding acquisition, Supervision, Writing – original draft, Writing – review and editing. All authors had access to the study data and reviewed and approved the final manuscript.

Ethics statement

Ethical approval for the study was obtained from the Regional and Institutional Human Medical Biological Research Ethics Committee, University of Szeged on 22 May 2022 (76/2023-SZTE RKEB). The research was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). Patient consent was waived by the Ethics Committee due to the retrospective nature of the study.

Data availability statement

The raw data that support the findings of this study are not publicly available, in accordance with the EU General Data Protection Regulation's (GDPR) guidelines for processing personal data. Data are only available upon reasonable request from the corresponding author, who is the owner of the dataset.

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