ADVANCED TREATMENT OPTIONS OF INFLAMMATORY BOWEL DISEASES AFTER ANTI-TNF FAILURE

Ph.D. Thesis

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Szeged

2025.

University of Szeged

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TABLE OF CONTENTS

LIST OF FULL PAPERS RELATED TO THE SUBJECT OF THE THESIS:

I. **Bacsur, Péter** ; Matuz, Mária ; Resál, Tamás ; Miheller, Pál ; Szamosi, Tamás ; Schäfer, Eszter ; Sarlós, Patrícia ; Iliás, Ákos ; Szántó, Kata ; Rutka, Mariann ; Bálint, Anita; Milassin, Ágnes; Fábián, Anna; Bor, Renáta; Szepes, Zoltán; Molnár, Tamás; Farkas, Klaudia. Ustekinumab is associated with superior treatment persistence but not with higher remission rates versus vedolizumab in patients with refractory Crohn's disease: results from a multicentre cohort study. THERAPEUTIC ADVANCES IN GASTROENTEROLOGY 15 : January-December Paper: 17562848221144349 , 18 p. (2022)
IF 4.2 *Q1 (Scopus – Gastroenterology)*

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IF 4.5 Q1 (Scopus – Gastroenterology)

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I. **Bacsur, Péter*** ; Wetwittayakhlang, Panu* ; Resál, Tamás ; Földi, Emese ; Vasas, Béla ; Farkas, Bernadett ; Rutka, Mariann ; Bessissow, Talat ; Afif, Waqqas ; Bálint, Anita ; Fábián, Anna ; Bor, Renáta ; Szepes, Zoltán ; Farkas, Klaudia ; Lakatos, Péter L* ; Molnár, Tamás*. Accuracy of the Pancolonic Modified Mayo Score in predicting the long-term outcomes of ulcerative colitis: a promising scoring system. THERAPEUTIC ADVANCES IN GASTROENTEROLOGY 17 Paper: 17562848241239606 , 11 p. (2024)
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IF 4.5 Q1 (Scopus – Gastroenterology)

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S C I E N T O M E T R I C S:

Number of full publications: 27
Cumulative impact factor: 101.591
Hirsch-index: 6

LIST OF ABBREVIATIONS

ADA – adalimumab
AEs – adverse events
ASUC – acute severe ulcerative colitis
CA – chronic activity
CCI – Charlson Comorbidity Index
CDAI – Crohn's Disease Activity Index
CD – Crohn's Disease
CRP – C-reactive protein
EIMs – extraintestinal manifestations
EMA – European Medicines Agency
FDA – Food and Drug Administration
GGT – gamma-glutamyl transferase
HR – hazard ratio
HLA – human leukocyte antigen
IQR – interquartile range
IFX – infliximab
IPAA – Ileal pouch–anal anastomosis
IV – intravenous
JAK1/3 – Janus activated kinase 1 and 3
LOR – loss of response
MRI – magnetic resonance imaging
MSC – mesenchymal stem cell
MAdCAM-1 – mucosal addressin cell-adhesion molecule-1
OR – odds ratio
PFCD – perianal fistulizing Crohn's disease
PDAI – Perianal Disease Activity Index
pMayo – partial Mayo score
PNR – primary nonresponse
SES-CD – Simple Endoscopic Score for Crohn's Disease
SFR –steroid-free remission
SPSS – Statistical Package for the Social Sciences
TFB – tofacitinib
TNF-α – tumor necrosis factor alpha
UST – ustekinumab
VDZ – vedolizumab

SUMMARY

INTRODUCTION The development of biological treatments has revolutionized the management of inflammatory bowel disease (IBD, Crohn's disease [CD], ulcerative colitis [UC]). Anti-TNF drugs are effective and safe in cases refractory or intolerant to conventional treatments; however, their long-term use is limited by primary and secondary failures. Vedolizumab (VDZ), ustekinumab (UST), and tofacitinib (TFB) have expanded the therapeutic arsenal, but robust real-world effectiveness and safety data was incomplete at the time of our investigations. Furthermore, evidence to support decision making on VDZ vs. UST after anti-TNF failure was also lacked. Mesenchymal stem cells (darvadstrocel) may be effective in the treatment of refractory perianal fistulizing Crohn's disease (PFCD), although clinical trial results were contradictory, and real-life experiences were also not available in sufficient quantities. Following the anti-TNF era, the treatment of IBD phenotypes, such as acute severe ulcerative colitis (ASUC), treatment-refractory CD, and PFCD, remains a challenge. Therefore, **we aimed** in our research work to analyze the effectiveness and safety of TFB in UC refractory to anti-TNF drugs, the comparative effectiveness and safety of VDZ and UST in anti-TNF refractory CD and the effectiveness and safety of darvadstrocel in PFCD patients refractory to anti-TND treatment in real-world settings.

METHODS We conducted three multicenter retrospective cohort studies. First, UC patients with a follow-up period of ≥ 6 weeks were enrolled consecutively in the ***tofacitinib*** (TFB) trial. Indications were categorized as ASUC and chronic active (CA) disease. Baseline demographic and clinical data were collected. Corticosteroid-free remission (SFR) rates, colectomy rates, and safety data were analyzed over a 52-week follow-up period. Second, CD patients who received ***VDZ or UST*** after anti-TNF failure were enrolled consecutively. Baseline was defined as the day of induction with VDZ or UST, and patients were followed until week 52. Clinical and biochemical activity, as well as SFR rates, were assessed. Concomitant medications, treatment escalation, comorbidities, hospitalizations, and surgeries were recorded during follow-up to identify predictors of treatment success. Third, patients with PFCD treated with ***darvadstrocel*** were enrolled consecutively and followed for 26-52 weeks. The primary outcome was perianal clinical remission at week 26 and 52. Secondary outcomes included clinical response rates, perianal disease activity (PDAI), patient satisfaction, and adverse events. Data were collected at baseline and at weeks 12, 26, and 52. Prediction of any outcomes were performed using logistic regression in all studies.

RESULTS ***In tofacitinib in ulcerative colitis study,*** a total of 391 UC patients (median age 38 [interquartile range, 28-47] years; follow-up period 26 [interquartile range, 14-52] weeks) were included. A total of 27.1% received TFB in ASUC. SFR rates were 23.7% (ASUC: 26.0%, CA: 22.8%) at week 12 and 41.1% (ASUC: 34.2%, CA: 43.5%) at week 52. The baseline partial Mayo score (odds ratio [OR], 0.850; $p = 0.006$) was negatively associated with week 12 SFR, while biologic-naïve patients (OR, 2.078; $p = 0.04$) more likely achieved week 52 SFR. The colectomy rate at week 52 was higher in ASUC group (17.6% vs 5.7%; $p < 0.001$) and decreased with age (OR, 0.94; $p = 0.013$). A total of 67 adverse events were reported, and 17.9% resulted in cessation of TFB. One case of thromboembolic event was reported. ***In the comparative VDZ vs. UST study*** a total of 161 UST- and 65 VDZ-treated patients completed the follow-up. No significant difference in clinical or biochemical remission rates was observed after induction between the two treatment groups; however, clinical remission rate at week 52 was higher in UST group [$p = 0.011$, OR = 2.39 with UST]. UST showed superior drug persistence than VDZ (86.5%, 57.9%, $p < 0.0001$). Drug failure rates were higher for VDZ (PNR rates: 21.54% and 4.97%, respectively, $p < 0.001$, OR = 8.267, $p = 0.001$). Hospital and surgical admission rates did not differ significantly. Only one adverse event occurred with VDZ at week 20, which led to drug cessation. ***In darvadstrocel in perianal fistulizing Crohn's diseadse study,*** 223 patients (male/female ratio: 0.48) were enrolled, in whom perianal clinical remission was achieved in 78.2% and 62.3% by weeks 26 and 52, respectively. Baseline PDAI score (OR 0.75), number of fistulas (OR 0.28), and number of weeks since preparation for surgery (OR 0.98) were associated with treatment failure. The clinical response rates were 84.8% and 79.8% at weeks 26 and 52, respectively. Improvement in subjective perianal symptoms was achieved in 77.8% and 78.4% of patients at weeks 26 and 52, respectively. Adverse events occurred in 13.5% of patients, with perianal abscesses and proctalgia being the most frequently reported.

CONCLUSIONS TFB may be effective for both moderate-to-severe UC and for patients with ASUC as a rescue therapy, as our observations suggest better colectomy rates in ASUC compared to IFX or cyclosporine. TFB should be considered as a first-line treatment for biologic-naïve patients in need of rescue therapy, or in lower-lines of therapy for chronic active disease, due to its outstanding efficacy and reassuring safety profile among available treatment options. Furthermore, UST was associated with superior drug persistence compared to VDZ at 1 year, a difference that was not influenced by comorbidities. Both UST and VDZ were found to be safe alternatives for patients refractory or intolerant to anti-TNF therapies, although their use in lower-lines of therapy is recommended. The effectiveness of darvadstrocel was found to

be higher than in clinical trials, though spontaneous fistula closure in placebo-treated patients remains high in the literature. In this context, patients with lower perianal clinical activity at baseline and fewer fistulas may achieve better outcomes. Additionally, tract preparation immediately before transplantation and appropriate use of antibiotics should be prioritized. To summarize our conclusions, novel biologic therapies, small molecules, and MSC-based treatments are both effective and safe following anti-TNF failure. However, numerous clinical characteristics must be considered when selecting the targeted population in order to achieve optimal results and improve patients' quality of life.

1 INTRODUCTION

Inflammatory bowel diseases (Crohn's disease [CD] and ulcerative colitis [UC]) are immune-mediated inflammatory conditions primarily affecting the gastrointestinal tract; however, several extra-intestinal symptoms further complicate patients' lives. Although a dysregulated immune response to a gut microbial antigen in genetically predisposed individuals is hypothesized, the exact pathomechanism of the diseases remains unclear. (1) Nevertheless, increased understanding of the immunological pathways underlying IBD has led to new therapeutic options, although the disease characteristics continue in a chronic and lifelong manner. (2)

Development of biological treatments have revolutionized treatment of IBD. They are produced by living cells organisms against key elements of the inflammatory pathways and may be used in moderate to severe disease refractory to conventional treatment. (3) Infliximab (IFX) is a chimeric monoclonal antibody, targeting the key cytokine of inflammation, tumor necrosis factor alpha (TNF-α), was the first biological drug approved by the European Medicines Agency (EMA) in 1999 for CD and in 2006 for UC. (4-6) Adalimumab (ADA) is a human type of anti-TNF-α antibody that reached to decrease the rate of immune-related (AEs) events in contrast with IFX and was approved by EMA in 2007 for the treatment of CD and 2010 for the treatment of CD. (7, 8)

Although several clinical and observational studies have reported the effectiveness of IFX and ADA in IBD, approximately 30% of patients do not experience any initial response to anti-TNF-α therapy due to primary nonresponse (PNR). (9, 10) Data suggest that approximately 25%–45% of patients show treatment failure of anti-TNF-α agents after an initial response (loss of response; LOR) within the first year. (11) Besides primary and secondary LOR, infusion-related AEs also limit the long-term use of anti-TNF agents.

Despite the revolution in IBD therapy brought about by the biologic era, the treatment of IBD phenotypes, such as acute severe ulcerative colitis (ASUC), treatment-refractory disease, and perianal fistulizing Crohn's disease (PFCD), remains a challenge to cure.

In total, 20–25% of UC patients experience severe flares requiring hospitalization due to ASUC, which is a life-threatening complication of UC with an urgent need for salvage treatment. (12) Intravenous corticosteroids can help avoid colectomy in the short term; however, 30–40% of ASUC patients do not respond to first-line salvage therapy and require IFX or cyclosporine to avoid colectomy. (13) Nevertheless, 30–40% of UC patients with at least one ASUC flare will

require colectomy during the disease course. (14) Tofacitinib (TFB) is an orally administered, non-selective small molecule inhibitor of Janus kinase 1 and 3 (JAK1/3) and has been used as an effective treatment for UC since the results of the OCTAVE study were published and the EMA approved it in 2017. (15) In Hungary, TFB was available for UC indications only under financial restrictions after 2019 by individual permission issued by the National Health Insurance Fund of Hungary. After 2022, it could be prescribed after anti-TNF failure, presumably due to its cost, as is the case in many other countries. Since TFB is a fast-acting treatment with a short half-life usability in ASUC has raised in few observational studies beside anti-TNF refractory cases of UC. (16, 17) ***Safety concerns have been raised in rheumatoid arthritis patients, while real-world data on TFB in chronic active UC indication was not available in 2021. Furthermore, there was also a lack of real-world robust evidence on its application in ASUC.***

In 2013, the GEMINI studies have proved the efficacy and safety of vedolizumab (VDZ) in UC and CD and got approval for IBD in 2014 by EMA. (18, 19) VDZ is a human G type immunoglobulin (IgG) targeting α4β7 integrins on lymphocytes surface resulting blocking interaction with mucosal addressin cell-adhesion molecule-1 (MAdCAM-1) on gut epithelium to avoid extravasation to the site of the inflammation. (20) Ustekinumab (UST) is an IgG type antibody against p40 subunit of IL-12 and IL-23 cytokines, which were approved by EMA in 2016 and 2018 in both CD and UC indications after a successful trials of UNITI and CERTIFI. (21, 22) Although, VDZ is available since 2015 and UST since 2018 based on individual permission, both drugs could be prescribed since 2019 according to financial authorization. In Hungary, at the time of our study in 2020, both drugs could be used as second- or third-line treatments after one or two anti-TNF failures or as first-line treatments if individual permission was obtained by the Insurance Fund of Hungary, however treatment choice was not supported by financial or scientific evidence. Although positive results from clinical trials of VDZ and UST in IBD patients after anti-TNF-failure have been published, while both medicines had become available, clear recommendations on sequencing treatments after anti-TNF drugs were still lacked. ***There were no available real-world data to determine whether integrin inhibition or IL-12/23 blockade is the better therapeutic option after anti-TNF failure***. Recently, two head-to-head trials analyzed the comparative effectiveness and safety of VDZ vs ADA in UC and UST vs ADA in CD (23, 24); however, a head-to-head randomized comparison of VDZ and UST is also still lacking.

PFCD complicates CD with fistulas between the anal canal or rectal segment and the perianal skin and occurs in 10–26% of CD patients. It is associated with extremely poor quality of life due to perianal pain, leakage, and functional restrictions. (25) According to the European Crohn's and Colitis Organization multidisciplinary approach is needed to treat PFCD including pharmacotherapy and surgical treatment options. (26) IFX is suggested at first line beside surgical closure techniques, however < 50% of PFCD patients could maintain response at week 52 according to ACCENT II trial. (27) Surgical options are limited by the potential destructive impact on anal continence. (28) Hence, there was an unmet need to identify additional targets and to develop novel biological and small molecule agents to cure PFCD.

Although IFX is recommended for achieving fistula healing, the optimal pharmacological treatment for PFCD is still lacking. The efficacy and safety of adipose-derived allogeneic mesenchymal stem cell (MSC) treatment (darvadstrocel) for PFCD were demonstrated in the ADMIRE-CD placebo-controlled clinical trial, where 51.5% of the treated patients showed combined clinical and radiological remission at week 24, compared to 35.6% in the placebo group. (29) The exact mechanism of action of darvadstrocel treatment is unclear; however, its immunomodulatory, anti-inflammatory, and reparative effects are believed to be involved. (30) Based on the results of the ADMIRE-CD trial, ECCO has recommended the use of MSC treatment as an alternative for PFCD. (28) In 2020, darvadstrocel treatment was authorized by the National Institute of Pharmacy and Food Safety of Hungary, however due to its cost, it was only be prescribed on the basis of an individual authorization in case of anti-TNF failure. ***Since then, only a few real-world studies assessing MSC treatment after anti-TNF failure have been published, and the positioning of darvadstrocel was complicated by the preliminary results of the ADMIRE-CD II trial, which showed no superiority over placebo.*** (31-34)

Despite the emergence of biological treatments and anti-TNF-α agents, acute severe ulcerative colitis, chronic refractory CD, and PFCD remain difficult to treat. Clear evidence on real-world usage of TFB in UC, UST and VDZ in CD, and darvadstrocel in PFCD after anti-TNF failure was not available when the studies were constructed.

2 AIMS

The global aim was to assess the effectiveness and safety of novel advanced treatments, especially TFB, UST, VDZ, and MSC in IBD in real-world setting after anti-TNF failure.

Study 1. We primary aimed to assess the effectiveness of TFB treatment in different indications of UC (ASUC and chronic activity [CA]) in a real-world, multicenter setting. In addition, we also aimed to identify predictive factors of effectiveness in different outcomes and to assess the prevalence of adverse events (AEs) during TFB therapy.

Study 2. Our primary aim was to compare the effectiveness and safety of VDZ and UST in patients with CD who had mostly failed anti-TNF treatment in a real-world, multicenter setting. The secondary aim was to identify predictive factors and comorbidities associated with treatment success and persistence.

Study 3. The overall objective of this study was to assess the long-term effectiveness and safety of adipose-derived MSC (darvadstrocel) treatment for PFCD in a real-world, multicenter setting.

3 PATIENTS AND METHODS

3.1 Study 1. To assess the effectiveness and safety of TFB treatment in different indications of UC (ASUC and chronic activity [CA]) in a real-world, multicenter setting.

3.1.1 Study design and participants

A retrospective, international, multicenter cohort study was conducted including 23 tertiary referral centers in Europe, Canada, and Israel. Data collection with collaborating centers was performed between February 1 and July 31, 2022. All investigators had to complete the unified database via medical record systems. The treatment protocols differ between the centers due to various funding protocols in different countries; consequently, tofacitinib is not allowed as a rescue treatment in ASUC or as a first-line treatment in UC in some of the involved centers. Baseline was defined as the first day of TFB induction, while 52 week of follow-up was set.

Consecutive patients with UC ≥18 years of age receiving tofacitinib were enrolled in our cohort. The indication of TFB was classified into ASUC according to the Truelove-Witts criteria (35) or CA/steroid dependence. Patients with a follow-up duration of < 6 weeks were excluded. In addition, patients with previous colectomy + ileal pouch–anal anastomosis or not obvious indication (marked as other) were excluded from further analysis.

3.1.2 Covariates, outcomes and definitions

The baseline demographic and clinical information comprised gender, age at UC diagnosis, date of UC diagnosis, disease extension, and severity at diagnosis (based on Montreal definitions [36]). The disease phenotype was evaluated based on the Montreal classification as well. (36) Clinical data comprised previous colectomy, extraintestinal manifestations (EIMs), previous biological treatments (IFX, ADA, golimumab, VDZ, UST), concomitant corticosteroid or thiopurine therapy, and indication of tofacitinib induction. Clinical (partial Mayo score [pMayo, [37]), endoscopic (Mayo endoscopic score [eMayo, [37]), and biochemical activity (C-reactive protein [CRP] and fecal calprotectin) and laboratory parameters (hemoglobin, serum iron, fer- ritin, transferrin saturation, thrombocyte count, cholesterol, triglyceride, and liver enzymes [aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase [GGT], and alkaline phosphatase]) were collected at week 0, weeks 2 to 6, weeks 8 to 14, weeks 22 to 30, and weeks 48 to 56.

The dose of TFB, the number and the type of AEs, the need of corticosteroid and/or immunomodulator treatment, hospitalization, and colectomy rates were obtained during the follow-up period as well.

The primary outcome was corticosteroid-free remission (SFR) rates at weeks 12 and 52. SFR was defined as a pMayo < 2 and CRP < 5 mg/L (38, 39) with no rectal bleeding and with no concomitant corticosteroid therapy.

Secondary outcomes were colectomy rates at weeks 12 and 52, PNR rates, LOR rates, and persistence of the treatment. PNR was defined as < 30% decrease in pMayo or ≥ 2 bleeding score at week 12, and LOR was defined as need of dose optimization or prolonged induction dose. We compared the secondary outcomes in ASUC and CA. The predictors of SFR, PNR, LOR, and colectomy-free survival rates were analysed.

The change in the clinical endoscopic activity index (pMayo, eMayo [endoscopic remission was defined as eMayo ≤ 1]), laboratory parameters monitoring disease activity, iron homeostasis, lipid metabolism, and liver enzymes were compared between visits during the admission of TFB. Liver enzyme elevation was considered as a level at least 1.5 times as high as normal.

The severity of infections was graded by the need of antibiotic or antiviral therapy. Severity of an AE was classified by the need of cessation of the treatment or dose reduction of therapy. AEs were also analysed in the relation with concomitant steroid therapy.

3.1.3 Statistical analysis

Statistical tests were performed using R statistical software version 4.1.1 (R Foundation for Statistical Computing) and SPSS software version 24 (IBM Corporation). Descriptive statistics are interpreted as median and interquartile range (IQR) or mean ± SD for continuous variables or numbers with percentage for categorical variables. Handling missing variables, the outcomes were analysed with the intention-to treat viewpoint. Change in continuous variables during the follow-up period was assessed with repeated-measures analysis of variance. Pearson's chi-square tests were performed to determine difference in frequency of categorical data. After identification of possible predictive factors of primary outcomes and secondary outcomes (colectomy, and PNR and LOR rates), multivariable logistic regression models were constructed (overall model fit was assessed by the Nagelkerke R^2 and goodness of fit was determined by performing the Hosmer-Lemeshow test). Kaplan-Meyer analysis was performed

to describe persistence on therapy and to compare the week 52 colectomy-free survival rate between ASUC and CA groups. Patients with incomplete follow-ups were included in the analysis as censored data. Values of $p < 0.05$ were considered statistically significant.

3.1.4 Ethical considerations

Ethical approval for the study was obtained from the Regional and Institutional Human Medical Biological Research Ethics Committee, University of Szeged (39/2022-SZTE RKEB; 5153). This study was conducted accord- ing to the principles of the Declaration of Helsinki (1975 Declaration of Helsinki, 6th revision, 2008), while the protocol was approved by the local ethics committee of the participating centres.

3.2 Study 2. To compare the effectiveness and safety of VDZ and UST in patients with CD who had mostly failed anti-TNF treatment in a real-world, multicenter setting.

3.2.1 Study design and participants

This was a retrospective multicenter cohort study that included five tertiary referral IBD centers in Hungary (*University of Pécs, Semmelweis University Department of Surgery and Interventional Gastroenterology, Semmelweis University First Department of Medicine, Military Hospital – State Health Center, University of Szeged*). The patients' data were collected consecutively from the medical records systems and stored in a uniform database. Baseline was defined as the day of the induction of VDZ or UST, while patients were followed until week 52. Data were obtained at induction of both agents, at 16–20 weeks after induction and at week 52. Patients ≥18 years old with an established diagnosis of CD who were receiving VDZ or UST therapy because of any contraindication of first-line anti-TNF agents or after failure of one or two anti-TNF agents were enrolled in each participating center. Patients were treated with UST or VDZ according to the current regulations of the National Health Insurance Fund of Hungary and the summary of the product characteristics. The patients received intravenous VDZ treatment with an induction regimen of 300 mg at weeks 0, 2, and 6 and received maintenance therapy with the same dose after induction at every 8weeks. An escalated regimen because of LOR was applied every 4 weeks. UST therapy was initiated with a weight-based intravenous infusion at baseline according to the following specifications (260 mg for <55 kg, 390 mg for 55–85kg, and 520 mg for >85kg). The first subcutaneous 90 mg induction dose was administered at week 8 followed by a subsequent maintenance dose of 90mg administered subcutaneously at every 4–12 weeks depending on disease activity. Enrolled patients provided written informed consent for both treatments.

Second-, third-, and fourth-line therapies were interpreted as the application of a different drug after the first, second, and third switch from the first-line biological agent, respectively.

3.2.2 Covariates and outcomes

Clinical and demographic baseline data, including sex, age at diagnosis, disease duration, location (using the Montreal classification [36]), disease behaviour (using the Montreal classification [36]), perianal phenotype, prior resections, and EIMs were collected. Data regarding the period of the prior anti-TNF treatment were also obtained. If patients received

both UST and VDZ treatments, data were obtained only until the first treatment. Patients with incomplete follow-up and no anti-TNF treatment were excluded.

At baseline, data, including UST and VDZ treatment lines, clinical activity based on the Clinical Disease Activity Index (CDAI [41]), biochemical activity based on CRP level, concomitant corticosteroid or thiopurine therapy and EIMs, were recorded. Clinical and biochemical activity, concomitant medications, EIMs, and perianal symptoms were obtained at 16–20 weeks after induction and at the end of follow-up at week 52. If the drug was terminated immediately after induction, a PNR was classified between weeks 16 and 20 because of the lack of initial efficacy. A LOR was defined as the occurrence of disease activity that led to treatment termination during the maintenance phase after effective induction or an escalated regimen was applied during treatment. EIMs and perianal complaints were evaluated based on both patients' and physicians' assessments using improved and not improved binary categories. The primary outcome was defined as SFR after the induction assessed at weeks 16–20 and at week 52. Remission was defined by clinical (CDAI < 150) and biochemical (CRP<10mg/L [38, 39]) activities. The primary outcome was used to identify the possible predictors of 1-year efficacy of both agents. The secondary outcome was defined as drug persistence at week 52.

Comorbidities were recorded and the Charlson comorbidity index (CCI), including age, myocardial infarction, chronic heart failure, peripheral vascular diseases, cerebrovascular accidents and/ or transient ischemic attack, dementia, chronic obstructive pulmonary disease (COPD), connective tissue disease, peptic ulcer disease, liver diseases, diabetes mellitus, hemiplegia, chronic kidney injury, solid tumor, leukemia, lymphoma, and acquired immune deficiency syndrome, was calculated at baseline. The CCI is a weighted index that is being validated for stratifying risk of comorbid conditions. (40) The CCI could range from a minimum of zero to a maximum of 33 points and was used to assess the effect of comorbidities on drug survival in combination with biological agents.

Hospitalization rates, surgical procedures, immunomodulator, and/or corticosteroid necessity during the follow-up due to disease activity were also obtained. The escalated regimens defined above were also recorded in case of both agents were used.

3.2.3 Statistical analysis

Statistical tests were performed using R statistical software version 4.1.1 (R Foundation, Vienna, Austria) and IBM SPSS software (IBM SPSS Statistics for Windows, Version 26.0, IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as the mean ± standard

deviation of the mean (SD) or median + interquartile range (IQR) for continuous variables and as the count + percentage for categorical variables. Normality was tested by visual interpretations. Continuous variables were tested via the Welch test or Mann–Whitney U-test for independent samples to compare differences between groups (after assumptions checked in cases of each test), whereas categorical variables were analyzed using the chi-squared test and Fisher's exact test to compare proportions of groups. Kaplan–Meyer analysis was performed to describe the persistence characteristics of a therapeutic effect of both agents. After identification of the possible predictive factors (based on univariate analyses) of primary outcomes, PNR and LOR multivariable logistic regression models were constructed (overall model fit was assessed by the Nagelkerke R^2 and goodness of fit was determined by performing the Hosmer–Lemeshow test). A multivariable Cox proportional hazards model was created to assess the effect of the CCI and type of any drug on persistence. Continuity of the hazard ratio (HR) over time was tested. Values of $p<0.05$ were considered to be indicative of statistical significance.

3.2.4 Ethical approval

The study was approved by the National Institute of Pharmacy and Nutrition according to the Scientific Research Ethics Committee of the Hungarian Medical Research Council's proposal (Registration No. OGYÉI/49083-1/2021). This study was conducted according to the principles of the Declaration of Helsinki (1975 Declaration of Helsinki, 6th revision, 2008).

3.3 Study 3. To assess the long-term effectiveness and safety of adipose-derived MSC (darvadstrocel) treatment for PFCD in a real-world, multicenter setting.

3.3.1 Study design, participants and administration

This retrospective multicenter cohort study was conducted in six tertiary inflammatory bowel disease (IBD) centres in three countries, including Israel, the Czech Republic, and Hungary. A sample of adult (age ≥ 18 years) CD patients who underwent MSC treatment (darvadstrocel) between January 1, 2019 and September 30, 2023, due to PFCD (high transsphincteric or suprasphincteric localisation, ≤ 2 internal and ≤ 3 external openings) refractory to traditional PFCD treatment (ineffectiveness of surgical fistula treatment and pharmacotherapy with antibiotics or immunomodulators or anti-TNFs within 6 weeks before the baseline) and with stable pharmacotherapy at least 3 months before inclusion were enrolled and examined. In this case, the baseline was defined as the day of the application of the MSC treatment, while follow-ups were conducted after 6–12 months. Patients with moderate to severe luminal activity (CDAI ≥220 [40]), active CD of the rectum, > 2 cm intra-abdominal abscess, concomitant rectovaginal fistula or deviating stoma, rectal or anal stricture and surgical intervention (except for surgical/seton drainage regarding perianal fistulas) were excluded from further analysis. Patients with multiple MSC treatments during the follow-up were also excluded. All patients provided their written informed consent to regular care.

Darvadstrocel was administered as an intralesional injection at the site of the perianal fistula after a preparation including rigorous curettage and seton placement according to the manufacturer's label. After the closure of the internal openings, approximately 120 million cells (5 million cells/mL) were administered during the procedure. All the participating centres were involved in the ADMIRE study and surgeons have treated subjects guided by ADMIRE experience. Adherence to the ADMIRE protocol was not a condition for participation in the study.

3.3.2 Covariates, outcomes and definitions

Data were collected into a uniform database at each centre (based on the medical history available in the medical record systems) and anonymously transferred to the coordinating center (*The University of Szeged*). The data regarding the preparation for surgery, including curettage of the fistula tracts and seton placement/revision before the baseline was obtained. Baseline demographic data (age, sex, date of birth, age at diagnosis), clinical data (disease localization

by Montreal classification (36), previous medications, current medications, previous surgery), and MSC surgery data were recorded at the baseline, while details of perianal clinical activity were measured at the baseline and weeks 12, 26 and 52 (if available). Due to the study design, data collection was allowed to be performed within 1 week of the reference timepoint.

Moreover, Parks's fistula classification was used (42), while luminal clinical activity was measured by CDAI (1.40), endoscopic activity was measured by the Simple Endoscopic Score for Crohn's Disease (SES-CD, [43]), and perianal complaints were objectivized by the Perianal Disease Activity Index (PDAI, 44). The C-reactive protein (CRP) level of the patients and modified Van Assche index (if MRI scans were performed, [45]) were recorded, while the patients' satisfaction levels and improvement of perianal symptoms were obtained at weeks 12, 26 and 52 by using a 3-point Likert scale (i.e., improved, not altered, worsened, [46]). Time-dependent variables, such as AEs, the reopening of a treated and closed fistula, and the occurrence of anal stenosis after treatment, were also recorded. Disease activity characteristics were recorded using prospectively followed patient records. Data collection was performed between February 1 and April 30, 2024.

The primary co-outcomes were the perianal clinical remission at weeks 26 and 52, defined by the closure of all external openings of the treated fistulas that were draining at baseline and assessed by a gastroenterologist/colorectal surgeon at regular visits. The secondary co-outcomes were the clinical response rates at weeks 26 and 52 (defined by the closure of at least one external opening of the treated fistulas and assessed by a gastroenterologist/colorectal surgeon at regular visits), whereas treatment failure was defined if no treated fistula tract was closed. The tertiary co-outcomes were the perianal clinical activity rates at weeks 12, 26, and 52 (defined by the PDAI score of > 4; [47]), the patients' satisfaction levels, and AEs requiring hospitalization (presented as incidence rates as frequency/100 patient-years). A sub-group analysis evaluating treatment experience was also conducted on the primary outcomes. Patients were stratified according to the overall experience of the treating centre and > 100 treatments with darvadstrocel was used as cut-off (high experience and low experience).

3.3.3 Statistical analysis

In this study, a power analysis was not performed, since it analyzed all eligible patients, and there was no control group, making a sample size calculation unfeasible. The descriptive statistics included the mean and standard deviation or the median and inter- quartile range (IQR) of the continuous variables, and the numbers and percentages of the categorical variables.

Normality was tested by using visual interpretations (histograms and quantile–quantile plots). After checking the assumptions, the groups described with the categorical variables were compared by using a chi-square test or Fisher's exact test, while the continuous variables were compared with independent samples t-tests. Potential covariates and confounders associated with the primary and secondary effectiveness outcomes were analyzed via univariable and multivariable logistic regression models. Specifically, the variables in the univariable analysis with a $p < 0.15$ were fitted and included in the multivariable analysis. Final multivariable models were obtained by forward selection using likelihood ratios. Moreover, the goodness of fit was analyzed by the Hosmer−Lemeshow test and the Nagelkerke R^2 was presented. Kaplan–Meier survival curves with a log-rank test were used to determine the characteristics of AEs over time. Cox proportional hazard models were also created to investigate the covariates associated with AEs. We performed a complete case analysis to reduce bias and to achieve the most accurate description of the cohort. Bonferroni correction was used to reduce multiple comparisons bias. A two-sided $p < 0.05$ indicated a statistically significant difference, while 95% confidence intervals (95% CI) were communicated. Statistical analysis was performed by using IBM SPSS software (Windows, Version 29.0, IBM Corp., Armonk, NY).

3.3.4 Ethical approval

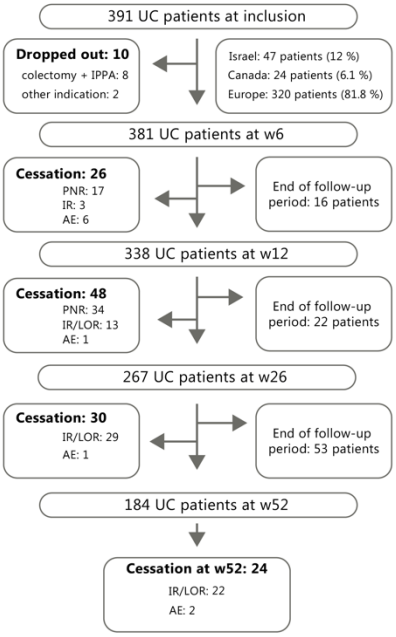
This study was approved by the National Institute of Public Health and Pharmacy based on the proposal of the Scientific Research Ethics Committee of the Hungarian Medical Research Council (Registration No. NNGYK/GYSZ/12796-4/2024). This study was conducted according to the principles of the Declaration of Helsinki (1975 Declaration of Helsinki, 6th revision, 2008), while the protocol was approved by the local ethics committee of the participating centres. All the patients gave their written informed consent for regular health care.

4 RESULTS

4.1 Study 1. To assess the effectiveness and safety of TFB treatment in different indications of UC (ASUC and chronic activity [CA]) in a real-world, multicenter setting.

4.1.1 Patient characteristics

In total, 391 UC patients (male/female ratio 208/183; median follow-up period 26 weeks [IQR: 14-52]) were included. The median age was 38 years (IQR: 28-47), and the median duration of disease was 7 years (IQR: 4-12). Flowchart of included patients are presented in ***Figure 1.***



1. Figure Study flowchart of included patients. Abbreviations: AE: adverse event, IR: ineffective response, LOR: loss of response, UC: ulcerative colitis; w: week

Almost two thirds of the patients had pancolitis (64.7 %). The main indication of TFB were CA (70.1%) and ASUC (27.1%). Further 2.8% of patients received TFB marked as other indication. The colectomy + IPAA surgeries were 2.0% of the patients; thus, they received TFB due to pouchitis. All patients received an induction dose of 20 mg/die. The vast majority of the cohort received anti-TNF treatment previously (83.6%; IFX: 74.9%, ADA: 39.1%, and GOL: 0.8%), and two thirds of the patients VDZ (64.2%). TFB was used in biological naïve patients in 11.8% of patients. Baseline demographic characteristics by groups are summarized in ***Table 1.***

Baseline clinical activity indexes were the following: median pMayo was 7 (IQR: 5-8) and eMayo 3 (IQR: 2-3). Biochemical markers showed elevated CRP (CRP: 19.3 mg/L ± 26.6) and fecal calprotectin (measured in 189 patients [48.3%], mean 1559.7 µg/g ± 1356.0). At the initiation of TFB, 45.7% patients were on systemic corticosteroids.

Characteristics	Total number of patients (n= 391)	ASUC (n=106)	Chronic activity (n=274)
Age, *years, median (IQR)*	38 (28-47)	38 (29-48)	37 (28-46)
Sex, *male N*	208 (53.2 %)	45 (42.5 %)	156 (56.9 %)
pMayo, *median (IQR)*	7 (5-8)	7 (5-8)	6 (5-8)
eMayo, *median (IQR)*	3 (2-3)	3 (3-3)	3 (2-5)
CRP *(mg/L), mean (SD)*	19.3 ± 26.6	35.3 ± 36.82	13.5 ± 18.72
Fecal calprotectin *(µg/g), mean (SD)*	1559.7 ± 1345.9	2046.5 ± 1282.7	1361.9 ± 1351.8
Disease duration, *years, median (IQR)*	7 (4-12)	8 (5-12)	7 (3-12)
Follow-up period*, weeks, median (IQR)*	26 (14-52)	26 (14-52)	39 (14-52)
Disease extension* *, N (%)*			
Proctitis	10 (2.6 %)	3 (2.8 %)	7 (2.6 %)
Left sided colitis	125 (32.7 %)	34 (32.1 %)	90 (32.8 %)
Pancolitis	247 (64.7 %)	69 (65.1 %)	177 (64.6 %)
Previous colectomy + IPAA*, N (%)*	8 (2.0 %)		
Follow-up period, *weeks, median (IQR)*	26 (14-52)	26 (14-52)	39 (17-52)
Baseline concomitant treatment, *N (%)*			
5-ASA	206 (52.6 %)	55 (51.9 %)	148 (54.0 %)
Budesonide-MMX	58 (14.8 %)	20 (18.9 %)	36 (13.1 %)
Azathioprine	17 (4.3 %)	5 (4.7 %)	11 (4.0 %)
Methotrexate	7 (1.8 %)	2 (1.9 %)	5 (1.8 %)
Cyclosporine	6 (1.5 %)	1 (0.9 %)	5 (1.8 %)
Prednisolone/ Methylprednisolone	179 (45.7 %)	52 (49.1 %)	123 (44.9 %)
Previous biologic treatments, *N (%)*			
IFX	293 (74.9 %)	74 (69.8 %)	209 (76.3 %)
ADA	153 (39.1 %)	37 (34.9 %)	109 (39.8 %)
GOL	3 (0.8 %)	1 (0.9 %)	2 (0.7 %)
VDZ	251 (64.2 %)	64 (60.4 %)	179 (65.3 %)
UST	25 (6.4 %)	9 (8.5 %)	13 (4.7 %)
Therapeutic line*, N (%)*			
Biologic naive	46 (11.8 %)	21 (19.8 %)	25 (9.1 %)
Second line	89 (22.8 %)	22 (20.8 %)	65 (23.7 %)
Third line	147 (37.6 %)	31 (29.2 %)	113 (41.2 %)
Fourth line	97 (24.8 %)	28 (26.4 %)	65 (23.7 %)
Fifth line	12 (3.1 %)	4 (3.8 %)	6 (2.2 %)

1. Table Baseline demographic and clinical data of the cohort

Abbreviations: ASUC: acute severe ulcerative colitis, N: number, CRP: C-reactive protein, pMayo: partial Mayo score, eMayo: endoscopic Mayo score, ADA: adalimumab; GOL: golimumab; IFX: infliximab; IPAA: ileal pouch–anal anastomosis; N: number of patients; PSC: primary sclerosing cholangitis; SD: standard deviation; UST: ustekinumab; VDZ: vedolizumab.

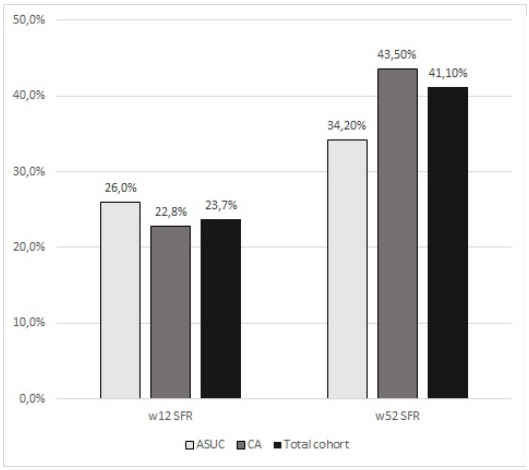
4.1.2 Corticosteroid-free remission rates

In total, 81 patients (23.7%) achieved SFR at week 12 and 117 patients (41.1%) achieved at week 52. The SFR at week 12 was 26.0% in the ASUC group, and 22.8% in the CA group, and no difference was observed between groups (p = 0.522). The SFR at week 52 was 34.2 % in the ASUC group and 43.5% in the CA group, and no difference was observed either (p = 0.352). Sustained steroid-free clinical remission rate was 17.9%. ***Figure 2.*** shows SFR rates at week 12 and 52.

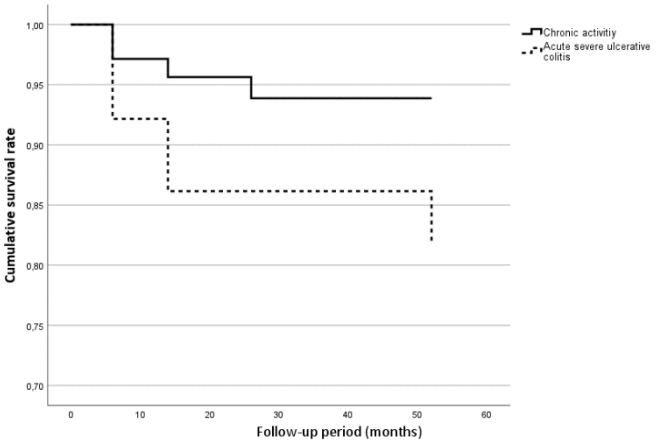
In the total cohort, a higher pMayo score at baseline was negatively associated with the week 12 SFR (OR = 0.850; p = 0.006), such as in the ASUC group (OR = 0.765; p = 0.012). In the

CA group, male sex (OR = 0.503; p = 0.04) and baseline CRP (OR = 0.962; p = 0.031) decreased the week 12 SFR rates (***Table 2.***).

Both in the ASUC group (OR = 5.378; p = 0.004) and in the total cohort (OR = 2.078; p = 0.04) biological naïve patients more likely achieved week 52 SFR, while in the CA group elder age (OR = 1.026; p = 0.016) seemed to be beneficial (***Table 2.***). Higher proportion of patients achieved 52-week SFR who received TFB in lower therapeutic line, close to the significance level (p = 0.061).



2. Figure w12 and w52 steroid-free remission rates in our cohort Abbreviations: ASUC: acute severe ulcerative colitis; CA: chronic activity; SFR: steroid-free remission rates; w: week



3. Figure Survival analysis regarding w52 colectomy rates between chronic activity and acute-severe colitis groups (p = 0.06)

	SFR predictive factors		OR	p value	95% CI	
Week 12	ASUC	constant	1.658	0.459	0.426	6.394
		Baseline pMayo	0.765	**0.012**	0.616	0.940
	CA	constant	0.589	0.078	0.324	1.058
		Male sex	0.503	**0.040**	0.260	0.967
		Baseline CRP	0.962	**0.031**	0.926	0.992
	Total cohort	constant	0.785	0.510	0.377	1.602
		Baseline pMayo	0.850	**0.006**	0.756	0.954
Week 52	ASUC	constant	0.341	**<0.001**	0.190	0.613
		Biologic naive	5.378	**0.004**	1.695	17.061
	CA	constant	0.290	**0.004**	0.124	0.678
		Age	1.026	**0.016**	1.005	1.047
	Total cohort	constant	0.632	**<0.001**	0.489	0.815
		Biologic naive	2.078	**0.040**	1.033	4.180
	Colectomy predictive factors		**OR**	**p value**	**95 % CI**	
Week 52	Total cohort	constant	0.374	0.198	0.084	1.670
		ASUC	4.829	**0.002**	1.810	12.886
		Age	0.946	**0.013**	0.906	0.988

2. Table Logistic regression to predict week 12 and 52 SFR, and w52 colectomy-rate in our cohort

After identification of possible predictive factors multivariate logistic regression models were constructed. Abbreviations: ASUC: acute severe ulcerative colitis; CA: chronic activity; CI: confidence interval; OR: Odds Ratio; SFR: steroid-free remission

4.1.3 Colectomy rates, PNR, LOR, and persistence of therapy

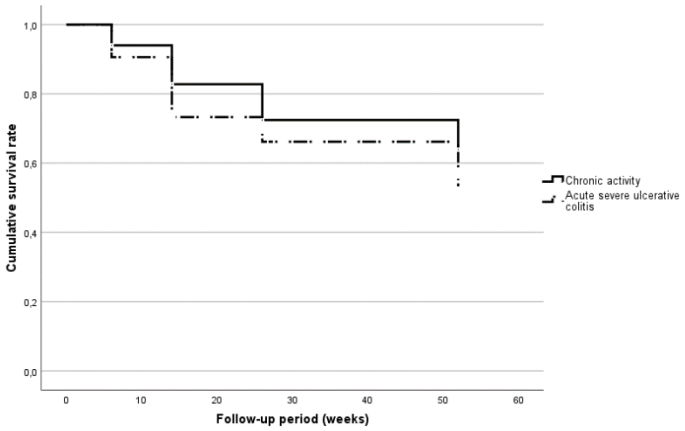
In total, the colectomy rate was 4.6 % at week 12, and no predictive factor was identified. In the ASUC group, the colectomy rate was higher (7.5% compared to 3.5% in the CA group); however, the difference was not significant (p = 0.115). No factor was found to be associated with colectomy rate either in the ASUC or in the CA group.

The week 52 colectomy rate was 8.0% in total, and the colectomy rate was significantly higher in the ASUC group compared to the CA group (17.6% vs 5.7%, p = 0.005). Based on the survival analysis (***Figure 3***.) more patients had colectomy during the follow-up period in the ASUC group (p = 0.008). In the total cohort, ASUC indication (OR: 4.829; p < 0.001) increased the colectomy rate at week 52, whereas older age decreased it (OR: 0.946; p = 0.013). No specific predictive factors were identified in the CA and ASUC groups (***Table 2.)***.

The PNR rate was 21.5% in the total cohort. The frequency of PNR was higher in the ASUC group (36.5% compared to 24.5%); however, it was not significant (p = 0.175). No marker was found to be associated with higher PNR rate.

In total, the prevalence of LOR was 54.1%, and it was more common in the CA group (58.5%) compared to ASUC (41.0%; p=0.006). In the LOR group, dose optimization was effective in 69 patients (37.5 %). No predictive factor was identified. At week 52 the dosage was distributed as follows: 5 mg/die 7 patients (3.9 %), 10 mg/die 94 patients (52.8 %), 20 mg/die 75 patients (42.1 %), 25 mg/die 1 patient (0.6 %), and 30 mg/die (0.6 %) 1 patient as well.

Patients with chronic activity indication seemed to remain on TFB for a longer period of time (35.3 weeks [±17.7] compared to acute severe UC (29.6 weeks [±18.8]; p = 0.07, ***Figure 3.)***.



3. Figure Drug persistence between various indications of tofacitinib (p = 0.07).

4.1.4 Change in clinical and biochemical activity

The clinical activity index decreased significantly ($p < 0.001$) from baseline level of 6.2 (± 2.2), to 3.5 (± 2.7) at week 12 and 1.8 (± 2.1) at week 52. Markers of biochemical activity decreased significantly during the treatment period. Baseline C-reactive protein was 19.34 µg/mL (±26.59), and it decreased to 10.15 µg/mL (± 18.86) at week 12, and to 6.42 µg/mL (± 11.46) at week 52 ($p < 0.001$). Fecal calprotectin decreased from baseline level of 1559.7 mg/g (± 1355.96) to 663.73 mg/g (± 654.08) at week 12 and to 313.76 mg/g (± 401.47) at week 52 ($p < 0.001$).

The level of serum albumin increased ($p < 0.001$) as well during the treatment, from a baseline level of 38.6 g/L (± 8.7) to 43.1 g/L (± 6.1) at week 52. An increase was already observed after 6 weeks ($p < 0.001$), as albumin was 41.2 g/L (± 5.4). Furthermore, platelet level altered during the treatment ($p = 0.002$), as it decreased from a baseline level of 372.9 G/L (± 136.0) to 311.2 G/L (± 109.8) at week 52.

4.1.5 Endoscopic response

Colonoscopy was performed in 312 cases (79.8%) before and in 242 cases after the admission of TFB (mean 22.5 [±16.1] weeks). In total, 12 patients (3.9%) were in endoscopic remission before TFB treatment, whereas 92 patients (43.0%) were in remission at the follow-up endoscopy, based on eMayo score ($p < 0.001$).

4.1.6 Adverse events

In total, 67 AEs (17.1%) were reported during the study. Based on our definition, 17.9% of them (12 cases) were severe AEs (3.1% of the total cohort). In 6 cases (50.0%), the cessation of TFB was due to infection (2 herpes zoster, 1 pneumonia, 1 perianal abscess, 1 carbuncle, and 1 clostridioides difficile infection), while in the other half of the cases, it was dyspnea (with no evidence of thromboembolic complications), vertigo, nausea, gastric pain, and skin rash (not specified as urticaria). Moderate AEs occurred in 13 cases (19.4%), while the remaining cases were mild (62.7%).

25 patients (6.4%) had an infection during TFB treatment, and in 48.0% of the cases (12 patients), the infection was moderate, but in 24.0% (6 cases; in the total cohort 1.5%), it was severe. The three most common infectious diseases were herpes zoster (24.0%), pneumonia (16.0%), and clostridioides difficile infection (16.0%). The infection rate was not influenced by

concomitant steroid therapy (p = 0.847). Two patients (0.5%) were reported to have malignant diseases (melanoma and cholangio-hepatic adenocarcinoma) during the administration of TFB therapy. Only one patient (0.25%) had a pulmonary venous thromboembolic event; however, this patient had cholangio-hepatic adenocarcinoma as well besides PSC, which was diagnosed nearly after one year of treatment. This patient has passed away due to the carcinoma. No more fatal event was reported.

The level of serum cholesterol was altered during the treatment (p = 0.006), as baseline 4.8 mmol/L (± 1.2) increased to 5.5 mmol/L (± 3.6). However, no similar change was observed in the triglyceride level (baseline 1.26 mmol/L to 1.30 mmol/L at week 52; p = 0.229).

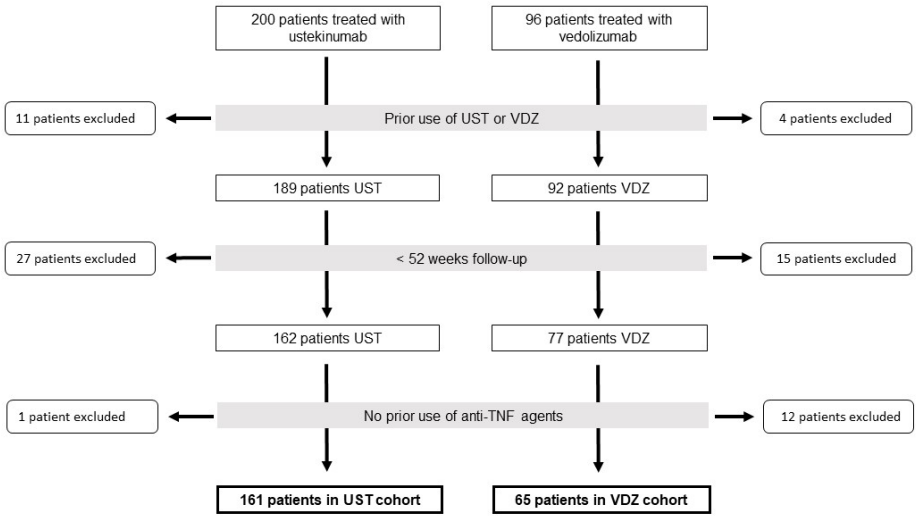
In addition, abnormal liver functions were also observed in a few cases, as 12 patients (3.1%) had novum GOT/GPT liver enzyme elevation, while 6 patients (1.5%) had novum γGT elevation. There was no overlap between these patients. Liver enzyme elevation was above 1.5-fold in 16 cases (88.9%), and in 2 cases, it was above 3-fold (in one patient the dose of TFB was reduced, while in the other case, statin therapy was initiated). Concomitant corticosteroid administration was not associated with elevated liver enzymes (p = 0.621). In total, no significant change was observed regarding the level of liver enzymes during the treatment period.

The AEs were mostly self-limiting, although in some cases, certain interventions were needed. We wish to highlight that all AEs were reversible. Treatment modification was needed in 25 cases, cessation of the TFB treatment was needed in 12.0%, dose reduction in 8.0%, or with specific treatment for the AE.

4.2 Study 2. To compare the effectiveness and safety of VDZ and UST in patients with CD who had mostly failed anti-TNF treatment in a real-world, multicenter setting.

4.2.1 Patient characteristics

Two hundred UST and 96 VDZ-treated patients were included in the study. Finally, after excluding data for sequential treatments with UST and VDZ, incomplete follow-up data, and data of patients without any prior anti-TNF treatment, the data of 226 patients were considered eligible for analysis (***Figure 4.***).



4. Figure Flowchart of exclusion depending on prior UST or VDZ treatment, follow-up period or no prior anti-TNX exposure. Abbreviations: UST ustekinumab, VDZ vedolizumab

In the UST and VDZ cohorts, 161 and 65 patients were eligible for analysis, respectively (median age: 36 and 35 years, male/female ratio: 57/104 and 21/44, median disease duration: 13.3 and 12.0 years, respectively). There were no differences in the baseline demographic data between the UST and VDZ cohorts. Among the baseline clinical characteristics of the patients, perianal disease phenotype was significantly more common in the UST cohort than in the VDZ cohort (44.7% and 24.6%, $p < 0.001$), respectively. Differences in treatment level, disease localization and behavior, disease activity parameters, prior bowel resections, and concomitant medications were not observed between the two groups at baseline. The most relevant extraintestinal symptom was arthritis in each group; however, neither the prevalence of EIMs nor any of the other baseline parameters differed significantly between the treatment groups. Prior IFX (infliximab) treatment was terminated in 61 UST- and 38 VDZ-treated patients due to LOR (37.9% vs. 58.5%, $p = 0.004$), and in case of 19.3% vs. 12.3% due to PNR ($p = 0.21$). Prior IFX exposure resulted in cessation in 23.6% and 7.7% ($p = 0.005$) in the UST and VDZ

treatment groups due to infusion associated reactions. In 9.9% of UST and 13.9% of VDZ treated patients' (p = 0.40) prior IFX treatment was terminated due to side effects. IFX treatment was stopped due to pregnancy in 3.1% and 4.6% (p = 0.58) of patients in the UST and VDZ cohorts. In patients treated with IFX previously, 6.2% in the UST and 3.1% in the VDZ groups (p = 0.34) the cessation of therapy was due to other patient associated causes. Prior ADA (adalimumab) was ceased due to LOR in 48.0% and 61.5% (p = 0.075) in the UST and VDZ groups, respectively. In 18.6% and 12.3% (p = 0.25) of patients in UST and VDZ cohorts with prior ADA treatment was terminated due to PNR. In addition, ADA treatment was stopped due to treatment-associated reactions in 13.0% and 10.8% (p = 0.64) in the UST and VDZ groups. Previous ADA therapy was terminated due to side effects in 7.5% and 4.6% (p = 0.44) in the UST and VDZ cohorts. Pregnancy resulted in cessation of ADA therapy in 3.7% and 6.2% (p = 0.42) of patients in UST and VDZ groups. While other patient associated termination occurred in 9.3% and 4.6% (p = 0.24) in the UST and VDZ groups. The baseline demographic and clinical characteristics of the cohorts are summarized in ***Table 3***.

4.2.2 Comorbidity prevalence and CCI at baseline

Data of 226 patients were available for assessing CCI at baseline. Nineteen patients (8.4%) had at least one comorbidity of which 11 (57.9%) were on UST and 8 (42.1%) were on VDZ therapy (p = 0.179).

In the cohort of patients with at least 1 comorbidity, 4 patients were >60 years old (21.05%), 5 were between 40 and 60 years old (26.32%), and 10 were <40 years old (52.63%). Of the four patients >60 years old, three were on VDZ treatment. Males were numerically more common in the comorbidity group than in the non-comorbidity group; however, statistical significance was not measured (52.6% vs. 32.9%, p = 0.083). There were no significant differences between groups according to the age, median disease duration, and follow-up time. The disease location was statistically similar in both groups (p = 0.982). The inflammatory phenotype was more common in patients with comorbidities than in those without comorbidities (73.7% vs. 47.3%), whereas penetrating disease was less frequent in patients with comorbidities (5.3% vs. 30.9%) (p = 0.04). There was no difference in the baseline disease activities between the comorbidity cohorts (CDAI p = 0.80, CRP p = 0.837). The baseline characteristics of patients with and without comorbidities are presented in ***Table 4.***

	Ustekinumab *(n = 161)*	**Vedolizumab** *(n = 65)*	***p value***
Treatment line[1], *N (%)*			
2.	50 (31.1)	20 (30.8)	0.566
3.	94 (58.4)	41 (63.1)	
4.	17 (10.6)	4 (6.2)	
Sex, male, *N (%)*	57 (35.4)	21 (32.3)	0.658
Age, *median (IQR)*	36 (15)	35 (18)	0.838
Disease duration, *years, median (IQR)*	13.34 (10.30)	12.00 (10.20)	0.566
Disease location, *N (%)*			
Ileum	22 (13.70)	11 (16.90)	0.903
Colon	52 (32.30)	23 (35.40)	
Ileocolic	75 (46.60)	31 (47.70)	
Upper GI involvement	12 (7.50)	0 (0)	
Disease behaviour, *N (%)*			
Inflammatory disease	78 (48.45)	34 (52.31)	0.837
Stricturing disease	35 (21.74)	14 (21.54)	
Penetrating disease	48 (29.81)	17 (26.15)	
Active perianal disease[2], *N (%)*	72 (44.7)	16 (24.6)	**<0.001**
Extraintestinal manifestations, *N (%)*			
Arthritis	36 (22.36)	14 (21.54)	0.893
Uveitis	0 (0)	0 (0)	-
Skin disease	6 (3.70)	0 (0)	-
Arthritis and skin disease	2 (1.24)	0 (0)	-
Prior bowel resection, *N (%)*	69 (43.4)	25 (38.5)	0.497
Prior anti-TNF exposure, *N (%)*			
Adalimumab OR infliximab	48 (29.81)	20 (30.77)	-
Adalimumab AND infliximab	111 (68.94)	45 (69.23)	
Disease activity, *mean (SD)*			
CDAI	244 (107.59)	229 (94.08)	0.332
CRP	24.60 (32.67)	23.13 (26.19)	0.735
Charlson comorbidity index, *N (%)*			
≤1	148 (91.9)	54 (83.1)	0.051
≥2	13 (8.1)	11 (16.9)	
Concomitant medication, *N (%)*			
corticosteroids	45 (27.95)	25 (38.46)	0.122
immunosuppressants	34 (21.12)	19 (29.23)	0.193

3. Table Baseline clinical and demographic characteristics of the patients.

[1]according to different drugs; [2]evaluated based on both patients' and physicians' assessments

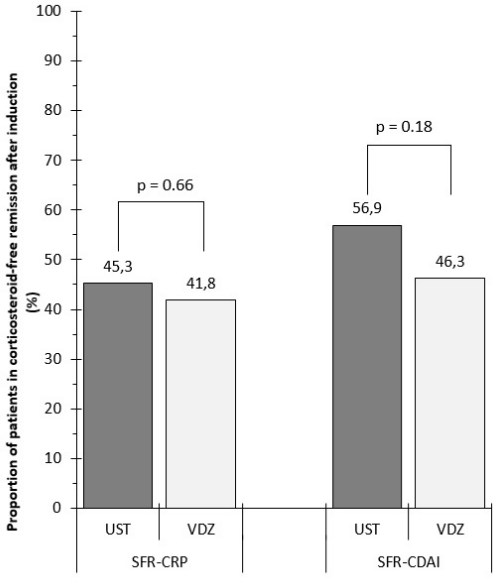
Abbreviations: N: number, CDAI: Crohn's disease activity index, CRP: C-reactive protein, SD: standard deviation of the mean, IQR: interquartile range

	Patients without comorbidities *(n = 207)*	Patients with comorbidities *(n = 19)*	*p value*
Treatment, *N (%)*			
Ustekinumab	150 (72.5)	11 (57.9)	0.179
Vedolizumab	57 (27.5)	8 (42.1)	
Sex, *male, N (%)*	68 (32.9)	10 (52.6)	0.083
Age, *years, median (IQR)*	35.25 (15.95)	38.00 (29.5)	0.166
Disease duration, *years, median (IQR)*	13 (10.38)	12 (9.5)	0.436
Follow-up time, *weeks, median (IQR)*	52 (0)	52 (0)	0.313
Disease location[1], *N (%)*			
Ileum	30 (14.5)	3 (15.8)	0.982
Colon	69 (33.3)	6 (31.6)	
Ileocolic	98 (47.3)	9 (42.1)	
Upper GI involvement	10 (4.8)	2 (10.5)	0.289
Disease behaviour[1], *N (%)*			
Inflammatory disease	98 (47.3)	14 (73.7)	**0.04**
Stricturing disease	45 (21.7)	4 (21.1)	
Penetrating disease	64 (30.9)	1 (5.3)	
Perianal disease[1], *N (%)*	98 (47.3)	7 (36.8)	0.38
Disease activity[1], *mean (SD)*			
CDAI	240 (104.48)	235 (100.27)	0.80
CRP	24.27 (31.31)	22.89 (24.77)	0.837

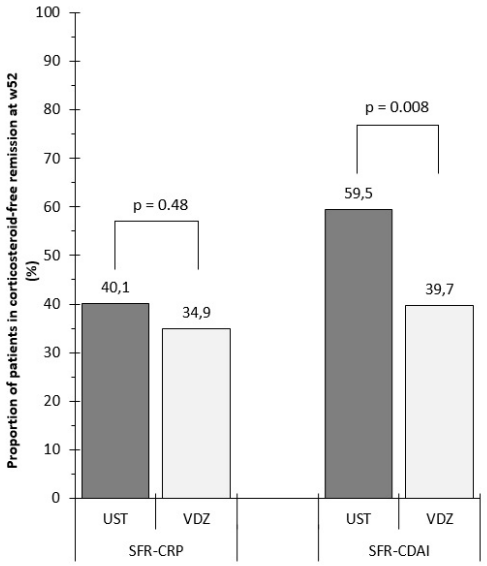
4. Table Comorbidity characteristics at baseline.

[1]At baseline

Abbreviations: N: number, CDAI: Crohn's disease activity index, CRP: C-reactive protein, SD: standard deviation of mean, IQR: interquartile range



5. Figure Proportion of patients achieving steroid-free remission (SFR) after the induction period (16–20 weeks) based on clinical (CDAI < 150) and biochemical (CRP < 10 mg/L) parameters. Abbreviations: p: significance level, UST: ustekinumab, VDZ: vedolizumab, SFR: corticosteroid-free remission, CDAI: Crohn's Disease Activity Index, CRP: C-reactive protein

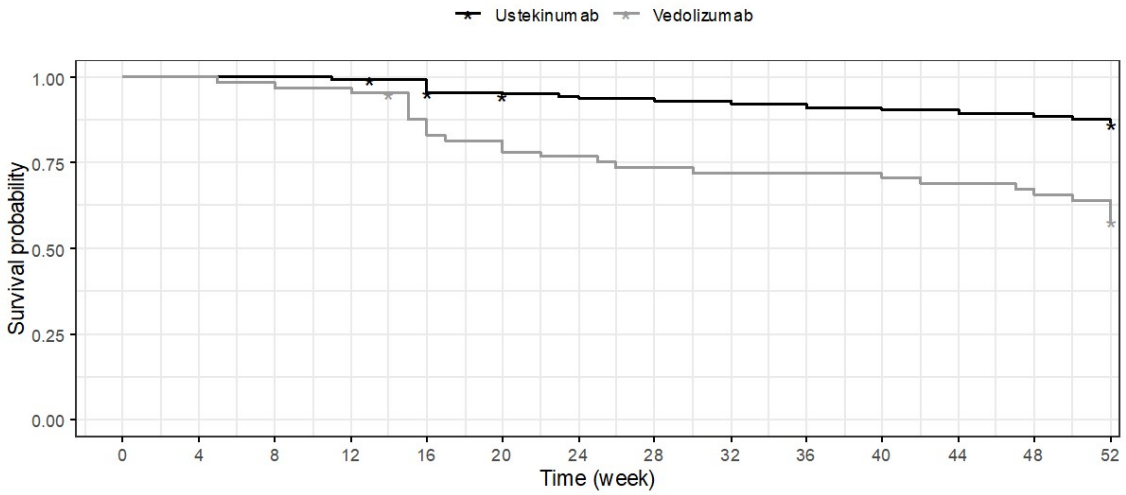


6. Figure Proportion of patients achieving steroid-free remission (SFR) at week 52 based on clinical (CDAI < 150) and biochemical (CRP < 10 mg/L) parameters. Abbreviations: p: significance level, UST: ustekinumab, VDZ: vedolizumab, SFR: corticosteroid-free remission, CDAI: Crohn's Disease Activity Index, CRP: C-reactive protein

Comorbidities did not differ significantly between UST and VDZ groups (6.79% vs. 12.3%, p = 0.179). There was a significant difference in the CCI between the VDZ and UST cohorts. More patients had a ≥1 higher score in the VDZ cohort than in the UST cohort (p = 0.046). CCI diseases were numerically higher in the VDZ group than those in the UST group (16.9 vs. 7.4, p = 0.059). The data referring comorbidities are presented in ***Table 4.*** The CCI score was not associated with drug persistence in our model (CCI HR = 0.977, p = 0.874).

4.2.3 SFR and therapy persistence

The clinical SFR rate was higher in the UST group than that in the VDZ group at week 52 (59.46 vs. 39.68, p = 0.008); however, neither biochemical SFR rates at week 52 (40.13 vs. 34.92, p = 0.48) nor SFR rates after the induction period differed significantly between the two groups (clinical: UST 56.94% vs. VDZ 46.30%, p = 0.18; biochemical UST 45.26% vs. VDZ 41.81%, p = 0.66). ***Figures 5. and 6.*** summarize these results. UST-treated patients were more likely to remain on therapy than VDZ-treated patients (UST: 86.5%, 95% confidence interval (CI) = 81.2%–92.0%; VDZ: 57.9%, 95%CI = 46.9%–71.3%; p < 0.0001) (***Figure 7.***).



7. Figure Kaplan–Meyer survival analysis showed the superiority in drug persistence of UST- versus VDZ-treated group (p = 0.001).

4.2.4 Predictors of SFR

In addition to the lines of treatment, the possible predictors of 52-week SFR were age, baseline CDAI and CRP levels, and CCI score. The possible effect of the drug type on achieving clinical remission was suggested (p = 0.008); however, differences in biochemical outcomes were not detected (p = 0.477). Differences between the groups who did and did not achieve SFR according to sex, comorbidity, combined immunomodulatory therapy, escalated regimen and disease duration were not significant.

According to the significant parameters mentioned above, the logistic regression models showed that drug type was a predictor of achieving clinical SFR (UST OR = 2.385, p = 0.011), while it was not confirmable on biochemical SFR (OR = 1.337, p = 0.403). By line of therapy, the probability of achieving SFR based on CDAI decreased with lines greater than third-line treatment (third-line vs. second-line, p = 0.007, OR = 0.38, fourth-line vs. second-line, p = 0.315, OR = 0.527). Baseline CDAI had a possible weak effect on the primary clinical outcome (OR = 0.997, p = 0.075). In our models, older age was a predictor of achieving SFR based on CRP (OR = 1.034, p = 0.037). The models' reliabilities were weak (Nagelkerke R^2: CDAI = 0.139 and CRP = 0.120). Model details are presented in ***Table 5.***

Outcome	Covariate	O.R.	95% CI on O.R.		Sig.
CDAI-SFR	Biological therapy	2.385	1.220	4.663	**0.011**
	As third-line treatment[1]	0.380	0.189	0.765	**0.007**
	As fourth-line treatment[1]	0.527	0.151	1.839	0.315
	Baseline CDAI	0.997	0.994	1.000	0.075
	Baseline CRP	0.997	0.988	1.007	0.614
	CCI score >1	0.745	0.215	2.585	0.643
	Age	1.019	0.988	1.051	0.242
CRP-SFR	Biological therapy	1.337	0.678	2.637	0.403
	As third-line treatment[1]	0.558	0.285	1.094	0.089
	As fourth-line treatment[1]	0.464	0.137	1.569	0.217
	Baseline CDAI	0.998	0.995	1.001	0.263
	Baseline CRP	0.988	0.974	1.001	0.077
	CCI score >1	0.569	0.158	2.054	0.389
	Age	1.034	1.002	1.067	**0.037**
LOR	Biological therapy	2.599	1.409	4.794	**0.002**
	Baseline CRP	1.000	0.997	1.002	0.840
PNR	Biological therapy	8.267	2.421	28.233	**0.001**
	Baseline CRP	1.012	0.999	1.024	0.062

5. Table Details of multivariable logistic regression models created on primary and secondary outomes

Abbreviations: OR: odds ratio, CI: confidence interval, CDAI: Crohn's disease activity index, CRP: C-reactive protein, SFR: corticosteroid-free remission, CCI: Charlson comorbidity index, PNR: primary nonresponse, LOR: loss of response

4.2.5 Therapy discontinuation, LOR, and drug safety

Treatment discontinuation due to any reason was more common in the VDZ cohort compared to UST group (VDZ 41.54% and UST 13.04%, p < 0.001) with a median duration of 28 (IQR 28) and 20 (IQR 32) weeks, respectively (p = 0.535). The PNR rate was more common in the VDZ cohort than in the UST cohort (21.54% and 4.97%; p < 0.001). The type of drug and baseline CRP were predictors of PNR (UST: OR 8.267, p = 0.001; baseline CRP: OR 1.012, p = 0.062). Details of multivariable models are available at ***Table 5.***

LOR was more common in the UST group compared to the VDZ cohort (61.5% and 36.9%, p < 0.001). Only biological agent was identified as a possible predictor of LOR. Therapy escalation was more commonly required by the UST-treated patients than by the VDZ-treated

patients (n = 97 (64.2%) vs. 15 (23.1%); p < 0.001). Escalation regimens of 12 to 8 weeks and 8 to 4 weeks were administered in 36 and 67 UST-treated patients (34.95% and 65.05%, respectively).

There was only one infusion-associated reaction resulting in treatment termination in the VDZ cohort at week 20. In the UST cohort, none of the patients presented drug-associated adverse events. Serious infections were not recorded in any of the treatment groups. In the VDZ cohort, one patient stopped treatment at week 16 because of pregnancy with an inactive disease.

4.2.6 EIMs, perianal disease and hospitalisations

The prevalence of EIMs did not differ at baseline between the UST and VDZ cohorts (27.32% and 21.53%, respectively; p = 0.367). During the induction period, existing complaints were improved in 13 patients in the UST cohort and in 3 patients in the VDZ cohort (29.55% vs. 21.43%, respectively; p = 0.554). During the 52-week follow-up, the symptoms of 14 UST- and 4 VDZ-treated patients improved from baseline (31.82% vs. 28.57%, respectively; p = 0.819).

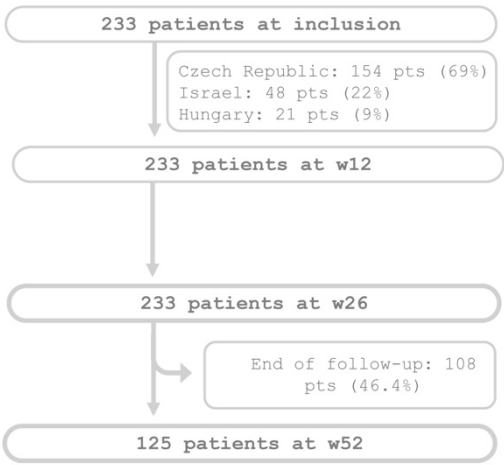
Active perianal disease was more common in the UST cohort than in the VDZ cohort at baseline (44.72% vs. 24.62%, p = 0.005). After the induction period, perianal symptoms were improved in 30 patients in the UST cohort and in 6 patients in the VDZ cohort (41.67% vs. 40.00%, respectively; p = 0.905). During the 52-week follow-up, perianal symptoms were improved in 39 patients in the UST cohort and in 5 patients in the VDZ groups (54.17% and 33.33%, respectively; p = 0.142).

Hospital admission was required in 10 UST- and 8 VDZ-treated patients because of relapse (6.2% and 12.3%, respectively, p = 0.126) at a mean of 27.6 and 13.5 weeks after inclusion (p = 0.022). Rates of hospitalization because of surgery did not differ between the treatment groups. Eighteen (11.2%) UST- and 13 (20.0%) VDZ-treated patients were admitted to surgery (p = 0.081) after a mean of 32.6 weeks from initiation of both drugs (p = 0.998). Resections were performed in all surgically hospitalized UST-treated patients; whereas seven patients required bowel resection (p = 0.633) and five patients needed perianal surgery in the VDZ group. None of the examined possible predictors differed significantly between the hospitalized and non-hospitalized groups and between the surgically treated and non-surgically treated groups.

4.3 Study 3. To assess the long-term effectiveness and safety of adipose-derived MSC (darvadstrocel) treatment for PFCD in a real-world, multicenter setting.

4.3.1 Patient characteristics

Overall, the data of 223 CD patients (male/female ratio: 0.48) was analyzed, with a median follow-up duration of 51.9 weeks [IQR 48–53]). Among the patients, 69% (154/223), 22% (48/223), and 9% (21/223) were from the Czech Republic, Israel, and Hungary, respectively. At inclusion, the median age was 39 years (IQR 33–49), and patients suffered from CD with a median duration of 13 years (IQR 7–21). Approximately three-quarters (75.7%) of the patients did not smoke at inclusion. In total, 69.1% of the patients were treated in high-volume tertiary centers. A flowchart of the enrolled patients is presented in ***Figure 8***.



8. Figure Flowchart of the patients' enrollment and follow-ups. Abbreviations: pts: patients; w: week.

The most common localization was ileocolonic (43.5%), while 40.7% of the patients had undergone prior bowel resection. The majority of the cohort (91.5%) were in clinical remission at the baseline. In addition, an immunomodulator was applied in 41.7% of the patients, while more than three-quarters were on anti-TNF treatment. Meanwhile, 57.4% of the patients had only one fistula tract at enrollment, with the majority transsphincteric fistulas. However, branching tracts were registered in 13.9% of the cases. Finally, more than half of the patients showed a PDAI score of > 4 (57.8%). Further details of the baseline clinical and demographic characteristics are presented in ***Table 6***.

Variables	**CD** (n = 223)
Follow-up duration, *weeks, median (IQR)*	51.9 (48-53)
Sex, *male (%)*	107 (48)
Age at inclusion, *years, median (IQR)*	39.0 (33-49)
CD disease duration at inclusion, *years, median (IQR)*	13 (7-21)
Prior bowel resection, *n (%)*	
small bowel segment	5 (2.2)
large bowel segment	17 (7.6)
ileocoecal	69 (30.9)
Disease localization, *n (%)*[+]	
ileal	71 (31.8)
colonic	55 (24.7)
ileocolonic	97 (43.5)
upper GI involvement	11 (4.9)
Disease activity	
CDAI, *mean (± SD)*	51.1 (53.1)
PDAI, >4, n (%)	129 (57.8)
CRP, *mg/l, mean (± SD)*	14.7 (9.5)
SES-CD, *mean (± SD)*	0.5 (1.1)
Prior advanced treatment, *n (%)*	
1 agent	63 (28.3)
2 agents	38 (17.0)
≥ 3 agents	15 (6.7)
anti-TNF	95 (42.6)
Description of fistulas, *n (%)*	
number of fistulas	
1	128 (57.4)
2	81 (36.3)
3	14 (6.3)
number of external openings	
1	127 (57.0)
2	79 (35.4)
3	17 (7.6)
number of internal openings	
1	177 (79.4)
2	46 (20.6)
branching fistula present	31 (13.9)
Classification of fistulas, *n (%)*[*]	
intersphincteric is present	33 (14.8)
transsphincteric is present	177 (79.4)
extrasphincteric is present	13 (5.8)
suprasphincteric is present	18 (8.1)
MRI was performed during FU	24 (10.8)

1. Table Baseline demographic and clinical characteristics of enrolled patients

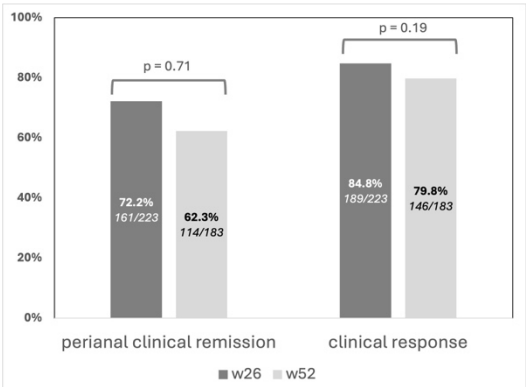
Montreal classification, *Parks classification, Abbreviations: CD: Crohn's disease, n: number of patients, IQR: inter-quartile range, SD: standard deviation of mean, CDAI: Crohn's Disease Activity Index, PDAI: Perianal Disease Activity Index, CRP: C-reactive protein, SES-CD: Simple Endoscopic Severity of Crohn's Disease, MRI: magnetic resonance imaging, FU: follow-up, TNF: tumor necrosis factor alpha

4.3.2 Effectiveness assessment

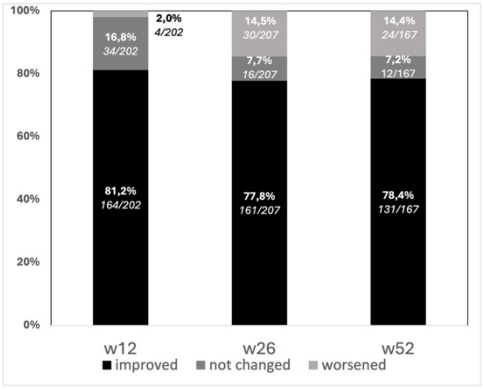
In total, the data of 100% and 82.1% of the patients were available at weeks 26 and 52, respectively. Perianal clinical remission was achieved in 72.2% (161/223) and 62.3% (114/183) of the patients by weeks 26 and 52, respectively. The clinical response rates were 84.8% (189/223) and 79.8% (146/183) at weeks 26 and 52. Neither the clinical remission rates (X^2 = 0.143; p = 0.71) nor the clinical response rates (X^2 = 1.722; p = 0.19) changed until week 52, respectively. ***Figure 10.*** presents the data regarding the proportion of patients achieving perianal clinical remission and response at weeks 26 and 52.

At the baseline, 57.8% (129/223) of the patients had perianal disease with PDAI score > 4. This rate decreased to 20.6% (41/199, X^2 = 60.638, p < 0.001), 17.2% (34/198, X^2 = 32.596, p < 0.001), and 19.6% (32/163, X^2 = 56.566, p < 0.001) at weeks 12, 26, and 52, respectively. Among week 26 responder patients, a similar decrease was found. However, the rate of perianal disease with PDAI score > 4 did not decrease among the patients with treatment failure at week 26. ***Figure 11.*** shows the proportion of patients with perianal disease with PDAI score > 4 at the baseline and weeks 12, 26, and 52, according to the treatment response at week 26.

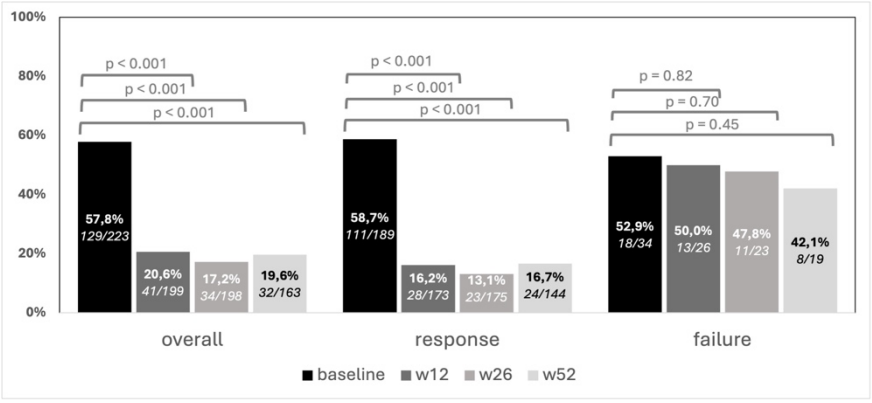
It is important to note that 81.2% (164/202), 77.8% (161/207) and 78.4% (131/167) of the patients experienced improvement in subjective symptoms, whereas 16.8% (34/202), 7.7% (16/207), and 7.2% (12/167) did not experience any change until weeks 12, 26, and 52, respectively. ***Figure 12***. presents the patients' experiences.



10. Figure The proportion of patients achieving perianal clinical remission and response at weeks 26 and 52. No significant difference was observed between the timepoints and endpoints. Abbreviations: p: significance level; w: week.



12. Figure The change in patients' symptoms during the follow-ups, measured on a three-point Likert scale. The majority of the treated patients experienced an improvement in perianal symptoms. Abbreviations: p: significance level; w: week.



11. Figure The proportion of patients with > 4 PDAI score for perianal disease during the follow-ups, stratified by achieving perianal clinical remission at week 26. Among the patients, perianal disease immediately decreased after treatment. Abbreviations: p: sign

4.3.3 Prediction of treatment efficacy

Week 52 clinical remission was negatively associated with antibiotic usage at MSC injection (OR 0.159, 95% CI 0.066–0.382), the level of the baseline PDAI score (OR 0.753, 95% CI 0.659–0.859), and the presence of branching fistulas (OR 0.417, 95% CI 0.172–1.011), while the week 26 remission outcome was coupled with the shorter period between preparation and transplantation surgery (OR 0.976, 95% CI 0.965–0.986) and the low number of fistulas at the baseline (OR 0.278, 95% CI 0.127–0.609). Achieving primary outcomes was observed more frequently in the centers with high-volume treatments in week 26 (82.5% vs. 49.3%, X^2 = 26.153; $p < 0.001$) and week 52 (72.0% vs. 41.4%, $X^2 = 15.815$; $p < 0.001$).

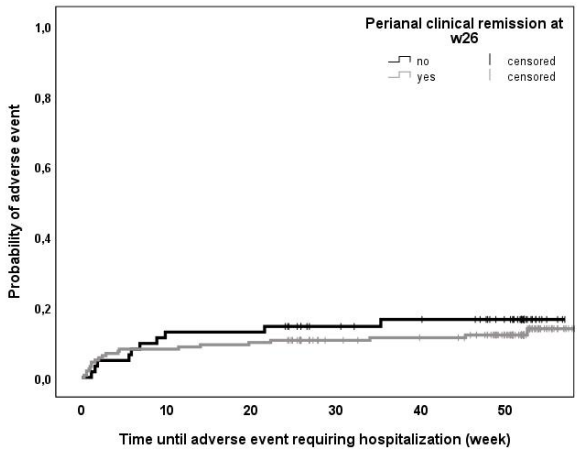
Clinical response rates at week 26 were associated with ileocolonic disease localization (OR 3.482, 95% CI 1.228–9.879), bowel resection history (OR 2.998, 95% CI 1.123–8.006), a high number of external fistula openings (OR 7.997, 95% CI 2.223–28.767), and prior usage of advanced treatments (OR 0.140, 95% CI 0.052–0.378).

Treatment failure at week 52 was associated with female sex (OR 0.392, 95% CI 0.157–0.980) and with longer periods between preparation and transplantation surgery (OR 0.992, 95% CI 0.984–0.999). ***Table 7.*** presents the results of the multivariable regression after model selection.

4.3.4 Safety analysis

Overall, 204 patient-years were recorded, of which 13.5% (14.7/100 PY) suffered from AEs requiring hospitalization during the follow-ups. Adverse events not requiring hospitalization were not observed. The median time until occurrence of an AE was 51.1 weeks (IQR 27.9–52.9) after treatment, while perianal abscesses, perianal pain, and perianal haematoma were registered the most. Meanwhile, the characteristics of AEs were similar between the groups,

stratified by achieving perianal clinical remission at week 26 (X^2 = 0.522, p = 0.47). The occurrence of AEs was also associated with a higher baseline PDAI score (HR 1.148, 95% CI 1.021–1.290), while active smoking (HR 0.227, 0.054–0.957) was coupled with decreased risk. ***Figure 13.*** displays the survival curve of the time to AEs, according to perianal clinical remission at week 26.



13. Figure Survival characteristics of adverse events requiring hospitalization during the follow-ups. The patients were stratified by achieving perianal clinical remission at week 26. Differences were not observed regarding outcome (X^2 = 0.522, p = 0.47).

Outcomes	Variables	Sig.	O.R.	95% CI	
clinical remission at w26	*Antibiotic use at injection*	**<0.001**	0.159	0.066	0.382
	PDAI	**<0.001**	0.753	0.659	0.859
	Branching fistula	0.053	0.417	0.172	1.011
clinical remission at w52	*Time between preparation and injection (wk)*	**<0.001**	0.976	0.965	0.986
	Number of fistulas, 1	**<0.001**			
	2	**0.001**	0.278	0.127	0.609
	3	**<0.001**	0.062	0.014	0.281
clinical response at w26	*Localization+, L1*	**0.027**			
	L2	0.936	0.957	0.329	2.785
	L3	**0.019**	3.482	1.228	9.879
	Prior resection	**0.028**	2.998	1.123	8.006
	Prior advanced treatment	**<0.001**	0.140	0.052	0.378
	Number of external openings	**0.001**	7.997	2.223	28.767
clinical response at w52	*Sex (female)*	**0.045**	0.392	0.157	0.980
	Time between preparation and injection (wk)	**0.030**	0.992	0.984	0.999

2. Table Multivariable logistic regression model to predict treatment effectiveness

+Montreal classification, Abbreviations: Sig: significance level, O.R.: odds ratio (exp(B)), 95% CI: 95% confidence interval, PDAI: Perianal Disease Activity Index, wk: week

5 DISCUSSION

Although newer targets for advanced therapy have been identified and the therapeutic arsenal is expanding, treatment strategies remain unsupported by robust evidence following anti-TNF failure. Therefore, there is an unmet need to establish data that can guide physicians in making optimal treatment choice. Multicenter collaboration in real-world observational trials involving a large number of patients can yield reliable data, while international partnerships help to achieve professional quality.

Our TFB in UC international, retrospective, multicenter study analyzed 391 UC patients worldwide, in which the week 12 steroid-free remission rate was 23.7%, in accordance with the w16–26 SFR rate of 25.0% in the meta-analysis conducted by Lucaciu et al. (48) However, our results was lower than the real-life meta-analysis of 44.3% conducted by Taxonera et al. (49), but exceeded the w8 remission result of the Octave 1 and 2 trials of 18.5% and 16.6%, respectively (15). Early efficacy did not differ between the CA and ASUC groups. Higher clinical activity reduced the chance of achieving week 12 SFR, whereas in CA group, higher CRP and male sex were negative predictors, in addition, older age was associated with increased chance of achieving week 52 SFR in CA. Male sex has previously been associated with reduced SFR rates in a meta-analysis (48).

Based on our findings, TFB is remarkably efficient as a rescue therapy in ASUC, as the week 12 colectomy rate was 7.5%, and the week 52 was 17.6%. Compared to international data, both IFX and cyclosporine had poorer short- and long-term outcome. Based on the study conducted by Laharie et al. (50), the 98- day colectomy rates were 17% in the cyclosporine and 21% in the IFX group, while Williams et al. (51) have found the 3-month colectomy rates to be 29% in IFX and 30% in cyclosporine. In this study, the 12-month outcome was also higher than experienced in our cohort, as in IFX, it was 35%, and in cyclosporine, it was 41%. These findings can be confirmed as well by the South-Korean cohort (52), where the 3-month colectomy rate was 26.1% in cyclosporine and 13.3% in IFX. However, the 12-month colectomy rate was comparable to our study in case of IFX (18.4%). Nevertheless, we emphasize the favorable effect of TFB knowing that the majority of the patients (almost 90%) did not receive it as a first line treatment. In addition, our study found, that biologic naïve patients more likely achieved SFR in the total cohort, and especially in patients with ASUC, and TFB admission in lower therapeutic line seemed to be more effective in achieving w52 SFR. These results are confirmed by the meta-analysis (49), where biologically naive patients had better response to therapy. Our findings did not confirm previous findings that low albumin

level and higher endoscopic Mayo score may be associated with higher colectomy rate. Furthermore, we found that the chance of colectomy is 4.8 times higher in ASUC.

In the total cohort, the 8.0% of week 52 colectomy rate is almost the same as in the meta-analysis (49). Our study confirmed the findings of Sandborn et al. (53) that older age increases the chance of remission, as we found it a protective factor both in colectomy and SFR (in the CA group); however, we would like to highlight the observations of Lichtenstein et al. (54) that SAEs, opportunistic infections, herpes zoster, malignancies, and major cardiovascular events are more frequent in elderly patients.

Primary non-response rates were slightly lower (21.5%) compared to previous data (26.0%) (55). No predictive factor was identified, in contrast with the retrospective observational cohort study conducted by Honap et al., where higher baseline CRP and younger age have been associated with increased PNR rates. We found no link between the number of previous biologic therapies and PNR, in accordance with existing data (55, 56).

Almost one in two patients had loss of response, and it was more common in case of chronic activity, which is probably due to the fact, that PNR was more frequent, and the follow-up time was shorter in case of ASUC. Based on recent publications, the frequency of LOR varies between wide ranges from 6.5% (56) to 72.3% (57), which suggests that approximately 50% can be realistic. However, extended induction dose and increase in dose were effective in one third of the patients. We wish to highlight that LOR is the least studied outcome of TFB admission in UC. All patients received TFB as 20 mg/die induction dose, and the maintenance dose was 10 mg/die, while the treatment escalation was mostly identical to the induction dose, however, in selected cases, higher dosage was used at the decision of the physician as well (25 mg/die and 30 mg/die, respectively).

Both AE and SAE rates were comparable with international data (49). In our cohort, herpes zoster was the most common infection in addition to pneumonia, clostridioides difficile, and perianal abscess. One in 4 patients, the infection was severe, and the affected patients made up half of the cases of cessation of TFB, and one patient passed away due to it. A thromboembolic event occurred in only one case; additionally, this patient had pancreas carcinoma meanwhile. In accordance with our results, patients in the OCTAVE induction 1 and 2 and in the OCTAVE sustain studies have had thromboembolic events. 5 thromboembolic events were reported (1 deep venous thrombosis and 4 pulmonary embolisms) and they had concomitant risk factors as

well (58). In summary, it can be concluded that AEs were predominantly mild and ceased spontaneously or with a reduction in dose or providing specific treatment.

Anti-TNF treatments have revolutionized the treatment of luminal CD; however, the majority of patients lose their response to them during the maintenance phase. VDZ and UST may be good alternatives to achieve mucosal or transmural healing and avoid further complications, but there is limited data on sequencing these drugs. ***Comparative VDZ vs. UST*** real-life multicenter nationwide study analyzed comparative data of UST- and VDZ-treated patients and demonstrated higher clinical SFR rates during the UST compared to VDZ treatments at week 52; however, biochemical SFR rates and SFR rates after the induction did not differ between the two groups. Remaining on therapy was more likely among the UST-treated patients than among the VDZ-treated patients. This finding may have been influenced by the fact that there was a significant difference in the frequency of dose optimization between the cohorts. The frequency of PNR was higher in the VDZ cohort than that in the UST cohort, whereas the frequency of LOR was higher in the UST cohort than that in the VDZ cohort. Our results also showed that using biologicals in a sequential way has negative impact on achieving clinical SFR.

Trials that have investigated the possible pharmacokinetic backgrounds of VDZ response loss have been contradictory. Ungar et al., in their multicentric-observational trial, did not find a consistent pharmacokinetic–pharmacodynamic correlation in the possible mechanism of LOR to VDZ, in contrast to anti-TNF drugs. (59) On the other hand, a systematic review and meta-analysis proved that escalated regimens could restore response to more than half of VDZ-treated patients. (60) The excess frequency of UST-escalated regimens could be explained by the fact that at the time of the introduction of UST, the standard subcutaneous dose was administered every 12th week in the maintenance phase, which later changed to a standard 8-week maintenance regimen per the label specification change.

Biemans et al. reported the significant superiority of clinical and biochemical SFR at week 52 for UST versus VDZ therapy from a Dutch propensity-score–matched trial. They did not prove the superiority of UST either after induction nor at week 12 and week 24. (61) A German single-center study showed that 78.9% of patients with CD and 68.1% of patients with UC continued VDZ treatment after week 52. (62) A meta-analysis that compared the efficacies of UST and VDZ in CD also collected data about clinical SFR and treatment persistence and found significant superiority of UST in both clinical SFR at week 52 and in drug persistence. (63) A recent multicentre-retrospective study from Italy displayed the equality of UST and VDZ in

terms of achieving objective remission among patients with anti-TNF refractory CD at week 52; however, clinical remission rates differed. (64) Our study found 1-year persistence rates of 86.5% for UST and 57.9% for VDZ treatment, which are higher than the rates found by Ylisaukko-Oja et al. (65)

In the present study, regression models were created to identify significant predictors of achieving SFR at week 52. The regressions showed that baseline UST treatment and lower treatment line were significant predictors of outcomes, although the Nagelkerke R^2 of the models indicated only weak correlations, whereas in patients with CD, a lower HBI was associated only with short-term SFR rates according the study by Mühl et al. (62) The PANIC study reported worsening persistence rates with increasing treatment line, which was seen in our cohort as well. (66)

Drug survival or long-term efficacy and safety are influenced by age and presence of any comorbidity. Previous studies found that the prevalence of comorbidities could predict the long-term treatment outcome in IBD via medication interactions, reduced adherence and poorer response to treatment. (67-68) In our study, the comorbidity frequency did not differ significantly between cohorts; however, Asscher et al. have reported higher comorbidity rates during VDZ treatment. In the present study, the CCI scores at baseline were higher in the VDZ cohort than those in the UST cohort, but the CCI score did not have a clear effect on drug survival in our model. Furthermore, age and comorbidity prevalence were not associated with SFR outcomes. The increased safety suggested by the different mechanism of action of VDZ in the presence of serious comorbidities explains the choice in our real-life setting.

UST and VDZ have been shown to have reassuring safety profiles. A meta-analysis of UST in patients with IBD found 16.7% incidence rate of adverse events, 8% infection rate and 3.9% serious infection rate. (69) A safety analysis of VDZ treatment from 46 studies has been reported. (70) The overall adverse event rate ranged from 1%–67% and the infection and serious infection rates ranged from 5%–24% and 4%–10%, respectively.

Hospitalization rates due to surgery or disease flare rates were 6.2% for UST and 10.4% for VDZ in our cohort, without any statistically significant difference which is in line with available data. (69) The improvement in EIMs differed between UST and VDZ because of their various mechanisms of action. In our study, UST did not show superior improvement of EIMs versus VDZ. A systematic review proved the efficacy of UST for the treatment of EIMs, especially for dermatological and rheumatological manifestations. (71) Only a few comparative clinical trials

have been reported. Perianal disease phenotype was more common in UST-treated patients, but there was no significant difference in symptomatic improvement between the treatment groups. Post-hoc analyses of clinical trials have provided only weak evidence that any investigated drugs could induce and maintain perianal fistula remission, so additional data are needed. (71-74)

Several other clinical trials have proven the efficacy and safety of new-generation biological agents in patients with IBD. In these trials, data were obtained from a selected population and financial restrictions, physicians' individual decisions and prior biological treatments, including biosimilars, were not examined. (74-75) There have been few head-to-head data comparisons of second- and third-line applications of both UST and VDZ in real-world study settings. (61, 76-77)

Both UST and VDZ were found to be safe and effective in patients with refractory CD, but both drugs were more effective in lower treatment lines. Patients with higher age and/or with more comorbidities could be treated by VDZ because of its mechanism of action, but EIMs limited the usability of VDZ.

Although several therapeutic options including surgical modalities have been introduced for the treatment of complicated CD phenotypes, PFCD remains difficult to treat. Quality of life is poor due to leakage, perianal pain, and other complications, while septic complications may pose a life-threatening risk. IFX is suggested to be introduced at first line in case of PFCD, < 50% of patients could maintain response at week 52, which highlight the unmet need for effective therapy to improve patients' quality of life. (27) ***In the darvadstrocel in PFCD study***, the effectiveness and safety of MSC treatment in PFCD was evaluated in a large multicenter cohort study, including 223 CD patients from tertiary IBD centers in a retrospective setting. The perianal clinical remission rates at weeks 26 and 52 were 72.2% and 62.3%, respectively, and were negatively associated with antibiotic usage, the baseline PDAI score, the interval between preparation and surgery, and with branching of the fistulas. AEs occurred in 13.5% of the patients, including perianal abscesses and pain. Instances of AEs were coupled with elevated baseline PDAI scores.

Several clinical trials were conducted to evaluate the efficacy and safety of MSC treatment among the CD patients with perianal fistulas. The ADMIRE CD placebo-controlled pivotal clinical trial included 212 CD patients. Among the 107 patients who were treated with darvadstrocel, a higher proportion (55%) achieved clinical remission (closure of all treated

external openings), compared to the placebo (43%) at week 24. (29) Interestingly, a long-term extension study of the ADMIRE CD trial reported an 80% clinical remission rate at week 52 in the treatment group. (78)

Meta-analyses and systematic reviews evaluated the overall efficacy of the darvadstrocel treatment, which showed superiority in fistula healing, compared to the placebo. (79-81) Overall, 72.2% of the patients were in clinical remission at week 26, while this proportion decreased to 62.3% at week 52. Although the clinical response rate was 84.8% at week 26, which was higher than that in the ADMIRE population (69% vs. 55%), the outcome was stricter (closure of at least 50% of the treated tracts). It should be highlighted, that the similarity of outcome results in our study are presumably due to the similarity of outcome definitions.

Nevertheless, the ADMIRE-II randomized-controlled trial displayed the non-superiority of MSC treatment, compared to the placebo (combined remission rate at week 24: 48.8% vs. 46.3%). (31) Although this questions the usefulness of the procedure, a full publication is not yet available. Meanwhile, even though the clinical remission rates were lower in the ADMIRE-II trial, higher effectiveness was observed in a real-world clinical setting. This is in line with the post-marketing INSPIRE registry and retrospective analysis of ADMIRE CD patients (INSPECT), indicating 76.6% and 67.4% clinical remission rates in one year. (82-83)

Both ADMIRE reports assessed the efficacy with combined clinical and radiologic remission (absence of fluid collections > 2 cm) as primary endpoints, which made it impossible to adequately compare them with our results. Moreover, MRI scans were only performed in 10.8% (24/223) of the patients, and a modified VanAssche score was only available in 7.2% of the patients (16/223). Thus, a statistical analysis, including radiological characteristics, was not performed. The lack of MRI data in a real-world setting may be explained by the costs, and poor availability of the procedure, and the obligatory need of experts for interpretation of the findings which was reported in an experts' opinion including Southeast Europe and Israel. (84)

However, due to the pragmatical design, control group was not able to be used to handle confounders. Nevertheless, to resolve the discrepancies between the efficacy of the clinical trials and the real-world data, several covariates and possible confounders were evaluated via univariable and multivariable regression analyses in this study to predict treatment success. First, a higher baseline PDAI score, antibiotic usage at treatment, a higher number of fistulas and branching fistula tracts, a delay of treatment after preparation surgery, female sex, and prior advanced treatment were associated with worse clinical outcomes. Second, although a higher

number of external openings seemed to predict treatment failure at week 26, this was not definite, due to the skewed distribution of the variables (three tracts in 7.6% of the patients). Third, prior usage of any advanced treatment can potentially select patients with more aggressive disease courses. However, the possible effect of pharmacological treatment before MSC treatment should not be overlooked. Based on these results, considering the baseline perianal clinical activity and the number of fistulas and branching tracts immediately after preparation for surgery may help to select patients with potentially better treatment outcomes. The impact of antibiotic use during MSC application on treatment outcomes may be questionable and controversial, since the exact pathological connection is lacking, however the interaction of antibiotics with MSC have been raised. (85) Extensive usage of systemic antimicrobial medications may be due to fear about infections by the surgical team, and preventive antibiotic usage should be avoided. Another possible reason for higher effectiveness may be the similar population descriptive features in our cohort, compared to the ADMIRE CD trials. The relatively low proportion of branching fistulas and high proportion of patients with mild perianal symptoms further reinforces the importance of population characteristics when comparing available data. Since a high proportion of the patients were on anti-TNF biologics, the clinical and biochemical activity parameters were low and fistula characteristics were comparable. Nevertheless, an accurate comparison with the population description of the overall ADMIRE study is necessary. Although, many of our data were based on a prospective data collection, real-world controlled research in prospective viewpoint considering different disease characteristics (perianal disease, multiple treatments, and deviating stoma) is needed to confirm our results.

In this study, our population encompassed 69.1% the patients treated in a high-volume tertiary center (where > 150 patients were treated with darvadstrocel). In this sub-cohort, the effectiveness was higher, compared to the rest of the cohort. Although not significant, this raises the question of the experience of the colorectal surgeons, gastroenterologists, and radiologists when selecting the ideal number of patients treated in a center.

In both ADMIRE reports, a relatively high proportion of patients achieved clinical remission in the control groups (> 40%) without darvadstrocel treatment. This result may be explained by the effect of the rigorous curettage of the fistula tracts performed before treatment. Hence, the importance of preparation for surgery should be emphasized in light of the high effectiveness rate of our cohort.

In the literature, assessments of patient-reported symptoms and quality of life are extremely limited. The exception was a French pilot study of 27 CD patients with perianal fistulas who showed significant improvement in their quality of life (CAF-QoL) after the treatment. This is in line with our study, in which 77.8%–81.2% of the patients experienced improvement of clinical symptoms, with a high level of treatment satisfaction. (33)

Moreover, in our cohort, the safety profile was reassuring, with an overall AE incidence rate of 14.7/100 PY. Abscesses and proctalgia were reported in most of the cases, which is in line with the pivotal ADMIRE CD trial. These findings suggest that MSC treatment is well-tolerated following its administration.

We have to note that several things are limiting the interpretation of our results. First of all, all three studies had retrospective design which made it impossible to draw exact conclusions, however the large patient numbers and multicenter settings allow to decrease potential bias during extrapolation. ***In case of TFB in UC study***, follow-up period did not reach the 52 weeks in all the cases, and thus, the extrapolation of the data could be narrowed. In case of ***comparative VDZ vs. UST study***, the distribution of data is skewed since anti-TNF agents are used as first-line therapy in IBD except in some special indications therefore the patients were receiving second- or third-line treatments with UST or VDZ. ***In case of darvadstrocel in PFCD study***, despite the high number of enrolled patients, the number of involved centers was relatively low and the treatment volume differed. Furthermore, it was not possible to specifically analyze the differences between the experiences of each center, which clearly impacted the treatment effectiveness and safety issues. Due to the pragmatic design, a control group was not used to independently handle the covariates associated with treatment such as spontaneous fistula closings. Moreover, due to the lack of sufficient number of results of cross-sectional imaging, analysis including MRI outcomes was not performed which limit the comparability of existing data.

There are several strengths to note. To handle potential covariates and confounders regression analyses were performed on primary outcomes in case of each study. Furthermore, relatively long follow-up periods and strict patient selection criteria were applied to obtain reliable data, while pragmatic endpoints helped to draw real-life conclusions.

6 CONCLUSIONS

TFB may be effective in both moderate to severe UC and in patients with ASUC as a rescue therapy. In addition, our observations suggest better colectomy rates in ASUC compared to IFX or cyclosporine. TFB treatment resulted in high rates of SFR and mucosal healing in both the short-term and the long-term even after anti-TNF and vedolizumab failure. Higher baseline disease activity and the number of previous biological therapies negatively influenced efficacy. TFB admission should be considered as a first line treatment in biologic naïve patients as a rescue therapy or in lower therapeutic line in chronic activity due to its outstanding efficacy among available therapeutic options and its reassuring safety profile. Serious adverse events were rare, and our results seem to support the assumption that thromboembolic events are associated with other risk factors.

Furthermore, our study results showed difference in clinical SFR but not in biochemical SFR, hospitalization, and surgery rates between patients treated with UST and those treated with VDZ. However, UST was associated with superior drug persistence versus VDZ at 1 year, which was not influenced by comorbidities. PNR was more common in VDZ-treated patients. UST and VDZ were found to be safe alternatives to anti-TNF refractory or intolerant patients, although use of these drugs in lower-lines of therapy is recommended.

Based on our results, the data regarding the effectiveness of the darvadstrocel treatment was higher than clinical trials. However, the spontaneous closure of fistulas in the placebo-treated patients remains high in the literature, presumably due to the rigorous curettage of the tracts. Moreover, the safety profile was reassuring, while the patients' satisfaction levels were high. Although precise conclusions may not be drawn, due to the retrospective setting and the lack of control group, the roles of several aspects of the preliminary assessment of treatment success and patient selection may be considered. In this regard, the patients with lower perianal clinical activity at the baseline and a lower number of fistulas may achieve better outcomes, while tract preparation immediately before transplantation and appropriate use of antibiotics should be prioritized. In sum, multidisciplinary medical and surgical treatment approaches are necessary for managing CD patients with perianal disease and further real-world data are needed.

In conclusion, TFB may be effective for both moderate-to-severe UC and for patients with ASUC as a rescue therapy. Therefore, it should be considered as a first-line treatment for biologic-naïve patients requiring rescue therapy, or as a treatment option in lower lines for chronic active disease. Furthermore, UST and VDZ are reasonable and safe alternatives in anti-

TNF refractory or intolerant CD cases, with comparable effectiveness, although their use is recommended in lower lines of treatment. Finally, the effectiveness of darvadstrocel was found to be higher than in clinical trials, though spontaneous fistula closure in placebo-treated patients remains high in the literature. In this context, patients with lower perianal clinical activity at baseline and fewer fistulas may achieve better outcomes.

To summarize our conclusions, novel biological therapies, small molecules, and MSC-based treatments are effective and safe following anti-TNF failure. However, numerous clinical characteristics should be considered when selecting a targeted population in order to achieve optimal results and improve patients' quality of life.

7 NEW FINDINGS

1. TFB is effective as rescue treatment as well as in chronic activity in UC, while therapeutic success is influenced by baseline clinical activity, older age, and male sex.
2. UST has higher persistence rate compared to VDZ, however no difference in effectiveness outcomes was observed.
3. Appropriate patient selection, fistula preparation and surgical expertise may help to achieve treatment success with darvadstrocel in PFCD.
4. All four drugs are safe alternatives after anti-TNF failure.

8 ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to all those who have contributed to the completion of my PhD thesis.

First, I would like to extend my sincere thanks to my supervisor, **Prof. Dr. Tamás Molnár**, for his invaluable support, guidance, and mentorship throughout my doctoral research. I am also deeply grateful to **Dr. Klaudia Farkas** for her continuous support, collaboration, and willingness to share her expertise. Their dedication and the considerable time they devoted to my progress were essential to the completion of my thesis. Special thanks go to my friend and colleague, **Dr. Tamás Resál**, for his unwavering support, inspiration, and tireless professional assistance.

I would also like to thank the director and head of the Department of Medicine at the University of Szeged, **Prof. Dr. Tamás Várkonyi**, and **Prof. Dr. Csaba Lengyel** for providing the resources, facilities, and research environment that enabled me to complete my thesis.

I am deeply grateful to the members of the Colorectal Study Group: **Prof. Dr. Ferenc Nagy, Prof. Dr. Zoltán Szepes, Dr. Kata Szántó, Dr. Bernadett Farkas, Dr. Renáta Bor, Dr. Anna Fábián, Dr. Zsófia Bősze, Dr. Emese Iványi, Dr. Anita Bálint, Dr. Mariann Rutka, Tibor Tóth**, and to all our collaborative partners, including **Dr. József Maléth**, **Dr. Boldizsár Jójárt** (MTA-SZTE Momentum Epithelial Cell Signaling and Secretion Research Group), **Dr. Pál Miheller** (Semmelweis University), **Dr. Patrícia Sarlós** (University of Pécs), **Dr. Tamás Szamosi** and **Dr. Eszter Schäfer** (Military Hospital - State Health Centre), **Dr. Ákos Iliás** (Semmelweis University), and **Dr. Mária Matuz** (Institute of Clinical Pharmacy). Without their collaboration and support, this work would not have been possible. I am also very grateful to **Dr. Mihály Zsilák-Urbán** for his extensive data, pharmacological support and ideas.

My sincere thanks also go to the assistant staff, particularly **Csilla Tóth-Káli, Brigitta Csorba, Krisztina Ördög**, and **Gabriella Pócsik**, for their invaluable administrative and logistical support throughout my research.

I would like to express my heartfelt thanks to **my family** for their unconditional love, understanding, and patience throughout the course of my PhD studies. Their unwavering support has been a constant source of strength.

Finally, I wish to express my gratitude to everyone who has contributed to the successful completion of this PhD work. Their support and encouragement have been deeply appreciated.

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10 ANNEXES

Co-author certification

I, myself as a corresponding author of the following publication(s) declare that the authors have no conflict of interest, and ***Péter Bacsur MD*** Ph.D. candidate had significant contribution to the jointly published research(es). The results discussed in her thesis were not used and not intended to be used in any other qualification process for obtaining a PhD degree.

2025. január 17.
date

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Tamás Resál MD., Ph.D.

The publication(s) relevant to the applicant's thesis:

Resál T, Bacsur P, Keresztes C, et al. Real-Life Efficacy of Tofacitinib in Various Situations in Ulcerative Colitis: A Retrospective Worldwide Multicenter Collaborative Study. Inflamm Bowel Dis. 2024;30(5):768-779. doi:10.1093/ibd/izad135

Co-author certification

I, myself as a corresponding author of the following publication(s) declare that the authors have no conflict of interest, and ***Péter Bacsur MD*** Ph.D. candidate had significant contribution to the jointly published research(es). The results discussed in her thesis were not used and not intended to be used in any other qualification process for obtaining a PhD degree.

12th January 2025
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The publication(s) relevant to the applicant's thesis:

Bacsur P, Shaham D, Serclova Z, et al. Evaluation of the Effectiveness and Safety of Mesenchymal Stem Cell Treatment in Fistulising Crohn's Disease: An International Real-Life Retrospective Multicentre Cohort Study. Aliment Pharmacol Ther. 2025;61(2):335-345. doi:10.1111/apt.18359

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06/01/2025 — date

Daniel Shaham — author name

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