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

Ph.D. Thesis

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

I. **Bacsur, Péter** ; Matuz, Mária ; Resál, Tamás ; et al. 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)*

II. Resál, Tamás* ; **Bacsur, Péter***; Keresztes, Csilla ; et al. Real-Life Efficacy of Tofacitinib in Various Situations in Ulcerative Colitis : A Retrospective Worldwide Multicenter Collaborative Study. INFLAMMATORY BOWEL DISEASES 30 : 5 pp. 768-779. Paper: izad135 , 12 p. (2024). *IF 4.5 Q1 (Scopus – Gastroenterology)*

III. **Bacsur, Péter*** ; Shaham, Daniel* ; Serclova, Zuzana*; 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. ALIMENTARY PHARMACOLOGY & THERAPEUTICS 61 : 2 pp. 335-345. , 11 p. (2025). *IF 6.6 D1 (Scopus – Gastroenterology)*

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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
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

INTRODUCTION

Development of biological treatments have revolutionized treatment of inflammatory bowel diseases (IBD, Crohn's disease [CD] and ulcerative colitis [UC]). Infliximab (IFX) and adalimumab (ADA) were the first biological drugs used in IBD, targeting tumor necrosis factor alpha (TNF-α). Although several clinical and observational studies have reported the effectiveness of IFX and ADA in IBD, approximately 25-45% of patients experience treatment failure within one year due to primary nonresponse (PNR) or loss of response (LOR). 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.

Tofacitinib (TFB) is an orally administered, non-selective small molecule inhibitor of Janus kinase 1 and 3 (JAK1/3) and has been used in UC since 2017. ***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.***

VDZ is a human G type immunoglobulin (IgG) targeting α4β7 integrins to avoid extravasation, while ustekinumab (UST) is an IgG type antibody against p40 subunit of IL-12 and IL-23 cytokines. In Hungary, at the time of our study in 2020, both drugs could be used mostly as second- or third-line treatments after anti-TNF failure. However, both medicines had become available during our study in 2020, ***there were no available robust real-world data to determine whether integrin inhibition or IL-12/23 blockade is the better therapeutic option after anti-TNF failure***.

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, while the exact mechanism of action of darvadstrocel treatment is unclear. ***Since athe approval in 2020, 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.***

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.

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. 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. We aimed 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.

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. Our 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.

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

PATIENTS AND METHODS

1.1 Study design and participants

Study 1. A retrospective, international, multicenter cohort study was conducted including 23 tertiary referral centers. Data collection with was performed between February 1 and July 31, 2022. 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. The indication of TFB was classified into ASUC or CA/steroid dependence. Patients with a follow-up duration of < 6 weeks and with previous resection were excluded.

Study 2. This was a retrospective multicenter cohort study in Hungary and the patients' data were collected consecutively. 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.

Study 3. This retrospective, international multicenter cohort study was conducted in six tertiary IBD centers. 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 refractory to traditional PFCD treatment were enrolled. 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, active CD of the rectum, > 2 cm intra-abdominal abscess, concomitant rectovaginal fistula or deviating stoma, rectal or anal stricture and surgical intervention were excluded. Darvadstrocel was administered according to the manufacturer's label.

1.2 Covariates, outcomes and definitions

Study 1. Clinical and demographic data were obtained at baseline. Clinical (partial Mayo score [pMayo]), endoscopic (Mayo endoscopic score [eMayo), and biochemical activity (C-reactive protein [CRP] and fecal calprotectin) 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. The primary outcome was corticosteroid-free remission (SFR) rates at weeks 12 and 52. Secondary outcomes were colectomy rates at weeks 12 and 52, PNR rates, LOR rates, and persistence of the treatment. We compared the secondary outcomes in ASUC and CA. The predictors of SFR, PNR, LOR, and colectomy-free survival rates were analyzed. AEs were also analyzed.

Study 2. Clinical and demographic baseline data were collected. 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), biochemical activity based on CRP level, concomitant corticosteroid or thiopurine therapy were recorded. Clinical and biochemical activity, concomitant medications 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. 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) 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) was calculated at baseline.

Study 3. The data regarding the preparation for surgery, including curettage of the fistula tracts and seton placement/revision before the baseline was obtained. Baseline demographic, clinical, 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). Moreover, Parks's fistula classification was used, while luminal clinical activity was measured by CDAI, endoscopic activity was measured by the Simple Endoscopic Score for Crohn's Disease (SES-CD), and perianal complaints were objectivized by the Perianal Disease Activity Index (PDAI). Time-dependent variables were also recorded. 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. The secondary co-outcomes were the clinical response rates at weeks 26 and 52. The tertiary co-outcomes were AEs requiring hospitalization.

1.3 Statistical analysis

Statistical tests were performed using R statistical software version 4.1.1 (R Foundation for Statistical Computing) and IBM SPSS software (IBM SPSS Statistics for Windows, Version 26.0, IBM Corp., Armonk, NY, USA). In all studies, power analyses were not performed, since it analyzed all eligible patients, and there were no control group, making a sample size calculation unfeasible. Descriptive statistics are interpreted as median and interquartile range (IQR) or mean ± SD for continuous variables or numbers with percentage for categorical variables. Normality was tested by using visual interpretations. Handling missing variables, the outcomes were analyzed with the intention-to treat viewpoint in the Study 1., and complete case analysis was performed in the Study 2. and 3. Change in continuous variables during the follow-up period was assessed with repeated-measures analysis of variance. Pearson’s chi-square tests or Fisher’s exact tests were performed to determine difference in frequency of categorical data, while the continuous variables were compared with independent samples t-tests, Welch test or Mann–Whitney U-test. After identification of possible predictive factors of primary or secondary outcomes, multivariable logistic regression models were constructed. Kaplan-Meyer analysis with LogRank test and Cox proportional hazards tests were performed to analyze time-dependent variables. Patients with incomplete follow-ups were included in the analysis as censored data. Values of $p < 0.05$ were considered statistically significant.

1.4 Ethical considerations

Ethical approval for all studies were obtained from the Regional and Institutional Human Medical Biological Research Ethics Committee, University of Szeged (39/2022-SZTE RKEB; 5153), or from the National Institute of Pharmacy and Nutrition according to the Scientific

Research Ethics Committee of the Hungarian Medical Research Council's proposal (OGYÉI/49083-1/2021), or from the National Institute of Public Health and Pharmacy based on the proposal of the Scientific Research Ethics Committee of the Hungarian Medical Research Council (NNGYK/GYSZ/12796-4/2024. Studies were conducted according to the principles of the Declaration of Helsinki (1975 Declaration of Helsinki, 6th revision, 2008), while the protocols were approved by the local ethics committee of the participating center

RESULTS

1.1 Patient characteristics

Study 1. 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). The main indication of TFB were CA (70.1%) and ASUC (27.1%). TFB was used in biological naïve patients in 11.8% of patients. Baseline clinical activity indexes were the following: median pMayo was 7 (IQR: 5-8) and eMayo 3 (IQR: 2-3).

Study 2. 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 ($p < 0.001$), 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.

Study 3. Overall, the data of 223 CD patients (male/female ratio: 0.48) were analyzed, while the median age was 39 years (IQR 33–49), and patients suffered from CD with a median duration of 13 years (IQR 7–21). 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.

1.2 Effectiveness outcomes

Study 1. 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. 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. Sustained steroid-free clinical remission rate was 17.9%. 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. 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. Higher proportion of patients achieved 52-week SFR who received TFB in lower therapeutic line, close to the significance level (p = 0.061). 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). 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. Patients with chronic activity indication seemed to remain on TFB for a longer period of time (p = 0.07*).*

Study 2. 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). More patients had a ≥1 higher score in the VDZ cohort than in the UST cohort (p = 0.046). The CCI score was not associated with drug persistence in our model (CCI HR = 0.977, p = 0.874). 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. UST-treated patients were more likely to remain on therapy than VDZ-treated patients (p < 0.0001). The 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. In our models, older age was a predictor of achieving SFR based on CRP (OR = 1.034, p = 0.037). 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). 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). LOR was more common in the UST group compared to the VDZ cohort (61.5% and 36.9%, p < 0.001). 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).

Study 3. 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 nor the clinical response rates changed until week 52, respectively. 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). Clinical response rates at week 26 were associated with 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).

1.3 Safety outcomes

Study 1. 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).

Study 2. 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.

Study 3. Overall, 204 patient-years were recorded, of which 13.5% (14.7/100 PY) suffered from AEs requiring hospitalization during the follow-ups. The occurrence of AEs was also associated with a higher baseline PDAI score (HR 1.148, 95% CI 1.021–1.290).

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.

Based on our ***TFB study***, 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., the 98- day colectomy rates were 17% in the cyclosporine and 21% in the IFX group, while Williams et al. 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 a South-Korean cohort. 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 a meta-analysis. In the total cohort, the 8.0% of week 52 colectomy rate is almost the same as in a meta-analysis. Our study confirmed the findings of Sandborn et al. 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. that SAEs, opportunistic infections, herpes zoster, malignancies, and major cardiovascular events are more frequent in elderly patients. Both AE and SAE rates were comparable with international data.

Anti-TNF treatments have revolutionized the treatment of luminal CD; however, the majority of patients lose their response to them during the maintenance phase. ***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. 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. 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. Regression analyses showed that baseline UST treatment and lower treatment line were significant predictors of outcomes, which was seen in the PANIC study. 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. 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, while the overall adverse event rate during VDZ treatment ranged from 1%–67% and the infection and serious infection rates ranged from 5%–24% and 4%–10%, respectively.

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. Meta-analyses and systematic reviews evaluated the overall efficacy of the darvadstrocel treatment, which showed superiority in fistula healing, compared to the placebo. 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. Nevertheless, the ADMIRE-II randomized-controlled trial displayed the non-superiority of MSC treatment, compared to the placebo. 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). 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. 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 retrospective designs 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 most of 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.

CONCLUSIONS

In conclusion, TFB may be effective for both moderate-to-severe UC and for patients with ASUC. Therefore, usage in lower therapeutic line may be considered. 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. In this context, patients with lower perianal clinical activity at baseline and fewer fistulas may achieve better outcomes.

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.

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