Study title: Real-life effectiveness and safety of tofacitinib and vedolizumab as a second-line therapy in anti-TNFs experienced patients with moderately to severely active ulcerative colitis

Study Acronym: VE2TO-UC

Protocol version: 2.0 **Date: 24/09/2022**

Sponsor: Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)

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STUDY SYNOPSIS	
Study title	Real-life effectiveness and safety of tofacitinib and vedolizumab as a second-line therapy in anti-TNFs experienced patients with moderately to severely active ulcerative colitis
Sponsor	Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)
Principal Investigator	Flavio Andrea Caprioli,
Protocol Version and Date	2.0 24/09/2022
Background and rationale	Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disease (IBD) involving the rectum and a variable extent of the colon1. For several years, the most advanced therapies for patients with moderate-to-severe UC were based on the blockage of tumour necrosis factor (TNF)-α. More recently, several new therapies, including the anti-integrin α4β7 vedolizumab (VDZ), the anti-p40 IL12/IL23 ustekinumab (UST), and the Janus kinase (JAK) inhibitors tofacitinib (TOFA), have been approved, leading to a relevant expansion of the therapeutic armamentarium for UC2. TOFA is the first approved, small molecule drug of its class – JAK inhibitors - for the treatment of moderate-to-severe UC. The OCTAVE clinical trials showed that in patients with moderately to severely active UC, therapy with TOFA at a dose of 10 mg twice daily was effective for induction of remission and mucosal healing. Maintenance therapy with TOFA at a dose of either 5 mg or 10 mg twice daily was effective in sustaining remission and mucosal healing3. Meta-analyses of real-world observational studies of TOFA in a highly refractory population of UC confirmed the good effectiveness of TOFA in UC and the known safety profile4,5. VDZ is an anti-α4β7 integrin antibody that inhibits the gut-homing of T-lymphocytes. The

	GEMINI clinical trial showed that in patients with moderate to severely active UC, therapy with VDZ is effective as both induction and maintenance therapy for moderately to severely active UC6. In addition, the VARSITY trial, which was the first head-to-head trial in UC, showed that VDZ was superior to adalimumab for the achievement of clinical remission and endoscopic improvement in patients with moderately to severely active UC7. A meta-analysis of real-world observational studies of VEDO has confirmed its effectiveness in inducing clinical response, clinical remission, corticosteroid-free clinical remission, and mucosal healing8. However, positioning different agents in the treatment course as first-line (in biologic-naïve patients) and second-line (in patients with prior exposure to TNF-a antagonists) therapy is a key knowledge gap. More specifically, the choice between TOFA and VDZ in the event of failure of anti-TNF inhibitors remains an open issue. Therefore, the treatment of choice is primarily based on clinician experience and expert opinion-based treatment algorithms. A recent network-metanalysis of randomized trials of adults with moderate-to-severe UC treated with TNF antagonists, VDZ, TOFA, or ustekinumab, as first-line or second-line agents showed the significantly superior efficacy of ustekinumab and TOFA over VDZ as second-line agents in inducing clinical remission (ustekinumab vs VDZ: OR, 5.99; 95% CI, 1.13–31.76 and TOFA vs VDZ: OR, 6.18; 95% CI, 1.003–8.00) and endoscopic improvement (ustekinumab vs VDZ: OR, 2.98; 95% CI, 1.20–7.41 and TOFA vs VDZ: OR, 3.85; 95% CI, 1.51–9.80) in patients with prior exposure to TNFα antagonists9. However, there are currently no published head-to-head real-world observational studies comparing the efficacy of TOFA and VDZ in this specific scenario. We address this knowledge gap through a retrospective real-life observational multicenter

	cohort study to compare the effectiveness and safety of TOFA and VDZ as a second-line biologic therapy in anti-TNFs experienced patients with moderately to severely active UC.
Study objectives	The main aim of the study is to compare in a large real-life observational multicenter cohort the effectiveness and safety of tofacitinib and vedolizumab as a second-line biologic therapy in anti-TNFs experienced patients with moderately to severely active ulcerative colitis (UC).
Study design	This is a retrospective real-life observational multicenter cohort study. All clinical records of UC patients in regular follow-up in each IBD referral centre participating in the study will be reviewed. Patients matching the following inclusion and exclusion criteria will be included. Inclusion criteria. Patients with a confirmed diagnosis of UC according to the current European Crohn's and Colitis Organization (ECCO) guidelines for at least 3 months; failure or intolerant to one or more anti-TNFs with moderate-to-severe active disease (defined as Partial Mayo Score [PMS] ≥5); left-sided or extensive UC requiring VDZ or TOFA as a second biological therapy, according to general clinical practice. Primary failure to anti-TNFs is defined as lack of efficacy or disease worsening occurring during the induction regimen and leading to therapy suspension immediately after. Secondary failure is defined as therapy suspension after an initial improvement, occurring at any time during maintenance. Intolerant patients are those who suspended anti-TNF after at least one dose for any occurring adverse event different from disease worsening. Exclusion criteria: - Subjects with inflammation restricted to the rectum (≤ 15 cm from the anal verge); - Subjects with severe active UC requiring hospitalization and IV steroids;

	- Subjects bio-naïve to biological therapy; - Subjects not treated with an anti-TNFs as first-line biological therapy; - Subjects receiving TOFA for an indication different from UC. Demographic data including gender, age, smoking status, and disease-related characteristics, such as disease duration, disease extent, and phenotype by Montreal Classification for UC, previous and concurrent UC treatments, previous anti-TNF alpha therapy, including data on primary/secondary failure and intolerance status, will be extrapolated from patient's clinical records and collected. VDZ will be administered at 300 mg IV at 0, 2, and 6 weeks for the induction and every 8 or 4 weeks as maintenance, according to standard practice. TOFA will be administered 10 mg twice daily for the induction and 5 mg bis in die (bid) as maintenance, according to standard practice. For patients receiving TOFA 5 mg bid, the dose could be adjusted to 10 mg bid following a clinical loss of response. Study design. Clinical conditions will be recorded when the indication to switch to either VDZ or TOFA is given and will be considered as baseline conditions. At baseline, disease activity assessed by PMS, steroid use and its dosage, C reactive protein (CRP), fecal calprotectin, and colonoscopy performed within 3 months before will be recorded. At 8 weeks, disease activity assessed by PMS, steroid use and its dosage, CRP, fecal calprotectin will be recorded if available. At 26 and 52 weeks, disease activity assessed by PMS, steroid use and its dosage, CRP, fecal calprotectin (if available), rectosigmoidoscopy or colonoscopy (if available), treatment persistence will be recorded. Any side effects, adverse events, and causes of treatment discontinuation reported in the clinical records will also be collected.

Study popolation	Adult anti-TNFs experienced patients with moderately to severely active UC treated with TOFA or VDZ as a second-line biologic will be the primary audience.
Methodology	In view of the efficacy data from two meta-analyses of real-world observational studies assessing clinical remission in a relatively unselected population of UC patients to reach a significant difference ($p<0.05$), assuming an 8-week clinical remission rate of 24% among patients treated with VDZ and 40% among patients treated with TOFA, a sample size of 264 patients (132 VDZ vs 132 TOFA) will be considered adequate to obtain a study power of 80%.
Statistical plan	Standard descriptive statistics will be used to analyse patients' characteristics. Continuous variables will be described as median and interquartile range (IQR). Categorical variables will be described as the number of cases and proportions. Comparisons between variables will be performed by chi-squared and by Mann-Whitney U tests. To minimize the effect of confounding variables, propensity score with inverse probability of treatment weighting (IPTW) will be used for the analysis of primary and secondary outcomes. Potential confounding variables considered for propensity score calculation will be age, age at diagnosis, sex, smoking habit, disease extension by Montreal classification, use of immunosuppressant and steroids at baseline, disease activity at baseline by PMS, *presence and type of extraintestinal manifestations, and* reason of anti-TNF discontinuation. Propensity score will be calculated by logistic regression using all confounding variables with treatment as the dependent variable. To minimize sample size inflation after weighting, stabilized weights will be calculated as (ρ/π) for VDZ-treated patients and ($(1-\rho)/(1-\pi)$) for TOFA-treated patients, where ρ is the probability of being

	treated with VDZ and π is the propensity score. Stabilized propensity score will be cut at the 1st and 99th percentile to exclude extreme outliners. IPTW will be independently calculated and applied for the entire cohort of analysed patients (i.e. all-patient cohort) to evaluate clinical outcomes at week 8 and 26, and for the sub-cohort of patients who will have baseline and week 26 objective evaluation to evaluate objective response and remission at week 26. All analyses will be based on an intention to treat basis with the last observation carried forward (LOCF). Statistical differences between treatment groups for primary and secondary dichotomous outcomes will be calculated by Person's chi-squared. Odds ratio (OR) and 95% confidence intervals (CI) will be estimated by logistic or linear regression models weighted by stabilized and truncated weights, with treatment as the single independent variable. $P<0.05$ will be considered statistically significant.
Ethical considerations	This study will be performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Milano 2 (Date 09/06/2022/No. 161704 parere 574_2022).
Study timeline	Project start date: 06/06/2022 Completion date of patients' enrollment: 31/03/2023 Data collection completion date: 29/09/2023 Data analysis: 31/10/2023 Presentation of the scientific report: 31/12/2023

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Statistician:	Daniele Noviello Phone: Fax: e-mail: noviellodaniele@gmail.com

AUTHORIZATIONS AND SIGNATURES

Study Title

AGREEMENT

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This document, however, can be made known to the designated Ethics Committee, or representatives authorized by the Investigator or the Health Authority provided that they are bound to its confidentiality.

The Principal Investigator's signature below confirms his agreement to this protocol and provides the necessary guarantees that:

1.This study will be conducted following all the clauses of the protocol and in accordance with the Helsinki declaration (Edinburgh 2000 with Explanatory note paragraph 29 from Washington 2002 and paragraph 30 from Tokyo 2004) and current legislation regarding clinical studies.

2. No partial or final data (written or verbal) will be published without prior agreement between the Investigator and the IgIBD

PRINCIPAL INVESTIGATOR SIGNATURE

Printed name:

Institution:

Signature _____ Date XX.XX.XXXX

TITLE

REAL-LIFE EFFECTIVENESS AND SAFETY OF TOFACITINIB AND VEDOLIZUMAB AS A SECOND-LINE THERAPY IN ANTI-TNFS EXPERIENCED PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS

INTRODUCTION

BACKGROUND/RATIONALE

Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disease (IBD) involving the rectum and a variable extent of the colon[1]. For several years, the most advanced therapies for patients with moderate-to-severe UC were based on the blockage of tumour necrosis factor (TNF)-α. More recently, several new therapies, including the anti-integrin α4β7 vedolizumab (VDZ), the anti-p40 IL12/IL23 ustekinumab (UST), and the Janus kinase (JAK) inhibitors tofacitinib (TOFA), have been approved, leading to a relevant expansion of the therapeutic armamentarium for UC[2].

TOFA is the first approved, small molecule drug of its class – JAK inhibitors - for the treatment of moderate-to-severe UC. The OCTAVE clinical trials showed that in patients with moderately to severely active UC, therapy with TOFA at a dose of 10 mg twice daily was effective for induction of remission and mucosal healing. Maintenance therapy with TOFA at a dose of either 5 mg or 10 mg twice daily was effective in sustaining remission and mucosal healing[3]. Meta-analyses of real-world observational studies of TOFA in a highly refractory population of UC confirmed the good effectiveness of TOFA in UC and the known safety profile[4,5].

VDZ is an anti-α4β7 integrin antibody that inhibits the gut-homing of T-lymphocytes. The GEMINI clinical trial showed that in patients with moderate to severely active UC, therapy with VDZ is effective as both induction and maintenance therapy for moderately to severely active UC[6]. In addition, the VARSITY trial, which was the first head-to-head trial in UC, showed that VDZ was superior to adalimumab for the achievement of clinical remission and endoscopic improvement in patients with moderately to severely active UC[7]. A meta-analysis of real-world observational studies of VEDO has confirmed its effectiveness in inducing clinical response, clinical remission, corticosteroid-free clinical remission, and mucosal healing[8].

However, positioning different agents in the treatment course as first-line (in biologic-naïve patients) and second-line (in patients with prior exposure to TNF-a antagonists) therapy is a key knowledge gap. More specifically, the choice between TOFA and VDZ in the event of failure of anti-TNF inhibitors remains an open issue. Therefore, the treatment of choice is primarily based on clinician experience and expert opinion-based treatment algorithms. A recent network-metanalysis of randomized trials of adults with moderate-to-severe UC treated with TNF antagonists, VDZ, TOFA, or ustekinumab, as first-line or second-line agents showed the significantly superior efficacy of ustekinumab and TOFA over VDZ as

second-line agents in inducing clinical remission (ustekinumab vs VDZ: OR, 5.99; 95% CI, 1.13–31.76 and TOFA vs VDZ: OR, 6.18; 95% CI, 1.003–8.00) and endoscopic improvement (ustekinumab vs VDZ: OR, 2.98; 95% CI, 1.20–7.41 and TOFA vs VDZ: OR, 3.85; 95% CI, 1.51–9.80) in patients with prior exposure to TNFα antagonists[9]. However, there are currently no published head-to-head real-world observational studies comparing the efficacy of TOFA and VDZ in this specific scenario.

We address this knowledge gap through a retrospective real-life observational multicenter cohort study to compare the effectiveness and safety of TOFA and VDZ as a second-line biologic therapy in anti-TNFs experienced patients with moderately to severely active UC.

OBJECTIVES

The main aim of the study is to compare in a large real-life observational multicenter cohort the effectiveness and safety of tofacitinib and vedolizumab as a second-line biologic therapy in anti-TNFs experienced patients with moderately to severely active ulcerative colitis (UC).

METHODS

STUDY DESIGN

This is a retrospective real-life observational multicenter cohort study.

All clinical records of UC patients in regular follow-up in each IBD referral centre participating in the study will be reviewed. Patients matching the following inclusion and exclusion criteria will be included.

***Inclusion criteria**. Patients with a confirmed diagnosis of UC according to the current European Crohn's and Colitis Organization (ECCO) guidelines for at least 3 months; failure or intolerant to one or more anti-TNFs with moderate-to-severe active disease (defined as Partial Mayo Score [PMS] ≥5); left-sided or extensive UC requiring VDZ or TOFA as a second biological therapy, according to general clinical practice. Primary failure to anti-TNFs is defined as lack of efficacy or disease worsening occurring during the induction regimen and leading to therapy suspension immediately after. Secondary failure is defined as therapy suspension after an initial improvement, occurring at any time during*

maintenance. Intolerant patients are those who suspended anti-TNF after at least one dose for any occurring adverse event different from disease worsening.

***Exclusion criteria**:*

- *Subjects with inflammation restricted to the rectum (≤ 15 cm from the anal verge);*
- *Subjects with severe active UC requiring hospitalization and IV steroids;*
- *Subjects bio-naïve to biological therapy;*
- *Subjects not treated with an anti-TNFs as first-line biological therapy;*
- *Subjects receiving TOFA for an indication different from UC.*

Demographic data including gender, age, smoking status, and disease-related characteristics, such as disease duration, disease extent, and phenotype by Montreal Classification for UC, previous and concurrent UC treatments, previous anti-TNF alpha therapy, including data on primary/secondary failure and intolerance status, will be extrapolated from patient's clinical records and collected.

VDZ will be administered at 300 mg IV at 0, 2, and 6 weeks for the induction and every 8 or 4 weeks as maintenance, according to standard practice. TOFA will be administered 10 mg twice daily for the induction and 5 mg bis in die (bid) as maintenance, according to standard practice. For patients receiving TOFA 5 mg bid, the dose could be adjusted to 10 mg bid following a clinical loss of response.

Clinical conditions will be recorded when the indication to switch to either VDZ or TOFA is given and will be considered as baseline conditions.

At baseline, disease activity assessed by PMS, steroid use and its dosage, C reactive protein (CRP), fecal calprotectin, and colonoscopy performed within 3 months before will be recorded. At 8 weeks, disease activity assessed by PMS, steroid use and its dosage, CRP, fecal calprotectin will be recorded, if available. At 26 and 52 weeks, disease activity assessed by PMS, steroid use and its dosage, CRP, fecal calprotectin (if available), rectosigmoidoscopy or colonoscopy (if available), treatment persistence will be recorded.

Any side effects, adverse events, and causes of treatment discontinuation reported in the clinical records will also be collected.

SETTING

All clinical records of UC patients in regular follow-up in each IBD referral centre participating in the study will be reviewed. Patients matching the inclusion and exclusion criteria will be included.

PARTICIPANTS

VARIABLES

The primary outcome is to compare the two treatments effectiveness at week 26 in terms of clinical remission, defined as PMS <3 and no subscore >1.

The secondary outcomes will be to compare the two treatments effectiveness in terms of

- corticosteroid-free clinical remission, biochemical remission (CRP ≤ 0.5 mg/dL and FCP level ≤250 μg/g, if available), and endoscopic response (decrease in endoscopic Mayo score of ≥1 compared with baseline, if available) at week 26 and week 52.
- Clinical response (decrease of at least 50% rectal bleeding and stool frequency) at week 8.
- treatment persistence at week 26 and week 52.

DATA SOURCES/ MEASUREMENT

All clinical records of UC patients in regular follow-up in each IBD referral centre participating in the study will be reviewed. Patients matching the inclusion and exclusion criteria will be included.

BIAS

Risk of including young non-comorbid patients on TOFA therapy and elderly comorbid patients on VDZ therapy. A propensity score matching will be used to minimize this potential bias.

STUDY SIZE

IN VIEW OF THE EFFICACY DATA FROM TWO META-ANALYSES OF REAL-WORLD OBSERVATIONAL STUDIES ASSESSING CLINICAL REMISSION IN A RELATIVELY UNSELECTED POPULATION OF UC PATIENTS TO REACH A SIGNIFICANT DIFFERENCE (P<0.05), ASSUMING AN 8-WEEK CLINICAL REMISSION RATE OF 24% AMONG PATIENTS TREATED WITH VDZ AND 40% AMONG PATIENTS TREATED WITH TOFA, A SAMPLE SIZE OF 264 PATIENTS (133 VDZ VS 133 TOFA) WILL BE CONSIDERED ADEQUATE TO OBTAIN A STUDY POWER OF 80%.

QUANTITATIVE VARIABLES

Spiegare come saranno gestite le variabili quantitative nelle analisi. Se applicabile, descrivere quali raggruppamenti sono stati scelti e perché

STATISTICAL METHODS

Standard descriptive statistics will be used to analyse patients' characteristics. Continuous variables will be described as median and interquartile range (IQR). Categorical variables will be described as the number of cases and proportions. Comparisons between variables will be performed by chi-squared and by Mann-Whitney U tests.
To minimize the effect of confounding variables, propensity score with inverse probability of treatment weighting (IPTW) will be used for the analysis of primary and secondary outcomes. Potential confounding variables considered for propensity score calculation will be age, age at diagnosis, sex, smoking habit, disease extension by Montreal classification, use of immunosuppressant and steroids at baseline, disease activity at baseline by PMS, presence and type of extraintestinal manifestations, and reason of anti-TNF discontinuation. Propensity score will be calculated by logistic regression using all confounding variables with treatment as the dependent variable. To minimize sample size inflation after weighting, stabilized weights will be calculated as (ρ/π) for VDZ-treated patients and ($(1-\rho)/(1-\pi)$) for TOFA-treated patients, where ρ is the probability of being treated with VDZ and π is the propensity score. Stabilized propensity score will be cut at the 1st and 99th percentile to exclude extreme outliners. IPTW will be independently calculated and applied for the entire cohort of analysed patients (i.e. all-patient cohort) to evaluate clinical outcomes at week 8 and 26, and for the sub-cohort of patients who will have baseline and week 26 objective evaluation to evaluate objective response and remission at week 26.
All analyses will be based on an intention to treat basis with the last observation carried forward (LOCF). Statistical differences between treatment groups for primary and secondary dichotomous outcomes will be calculated by Person's chi-squared. Odds ratio (OR) and 95% confidence intervals (CI) will be estimated by logistic or linear regression models weighted by stabilized and truncated weights, with treatment as the single independent variable. $P<0.05$ will be considered statistically significant.

OTHER ANALYSES

NA

SAFETY MANAGEMENT

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Milano 2 (Date 09/06/2022/No. 161704 parere 574_2022).

INFORMED CONSENT/ASSENT AND DATA PROCESSING

INFORMED CONSENT TO THE STUDY WILL BE ACQUIRED DURING THE FOLLOW-UP VISITS TO THE SINGLE REFERRAL CENTER. IN ADDITION, AN ADDITIONAL INFORMED CONSENT WILL BE ACQUIRED FOR THE RECORDING OF DATA ON THE IGIBD REGISTER.

CONFLICT OF INTEREST

Indicare gli interessi finanziari degli sperimentatori per ciascun sito di studio.

PUBLICATION/DATA SHARING POLICY

A. *PRINCIPAL INVESTIGATOR WILL BE RESPONSIBLE FOR STUDY DESIGN, DATA COLLECTION, DATA INTERPRETATION, MANUSCRIPT WRITING, LAST AUTHOR. INVESTIGATORS WILL BE RESPONSIBLE FOR DATA COLLECTION, MANUSCRIPT REVIEWING AND EDITING, CO-AUTHORS.*
B. *PRINCIPAL INVESTIGATOR WILL BE STUDY GUARANTEE AND DATA OWNER. DATA WILL BE SHARED UPON REASONABLE REQUESTS.*
C. We plan to submit preliminary data at the United European Gastroenterology Week 2022 and IG-IBD 2022. We plan to submit, in early 2023, the full paper to a mid-to-high impact journal, such as the *Journal of Crohn and Colitis*, *Alimentary Pharmacology and Therapeutics* or *Inflammatory Bowel Diseases*.

LITERATURE REFERENCES

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