NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study Information

Title	12- and 18-Month Outcomes and Long-Term Survival of Tofacitinib in Ulcerative Colitis
Protocol Number	A3921416
Version Identifier of the Final Study Report	1.0
Date	19 November 2022
EU Post Authorization Study (PAS) register number	EUPAS44985
Active substance	Tofacitinib citrate (ATC code L04AA29)
Research Question and Objectives	This retrospective cohort study will assess real-world clinical outcomes at 12 and 18 months after initiation of tofacitinib therapy for ulcerative colitis. Assess proportions of clinical remission and corticosteroid-free clinical remission at Week 52 and 78 after tofacitinib induction in a real-world cohort of patients with ulcerative colitis (UC).
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TABLE OF CONTENTS

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RedactedRedactedRedactedRedactedRedactedRedacted
Redacted

LIST OF IN-TEXT TABLES AND FIGURES

Annex 1. List of stand-alone documents

Not applicable

Appendix 4. STATISTICAL ANALYSIS PLAN

Not applicable

Appendix 5. SAMPLE CASE REPORT FORM (CRF) / DATA COLLECTION TOOL (DCT))

Not applicable.

Appendix 6. SAMPLE STANDARD SUBJECT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT (ICD)

Not applicable.

Appendix 7. LIST OF SUBJECT DATA LISTINGS

Appendix 7.4.1 Demographic Characteristics

Appendix 7.4.2 Disease Characteristics

Appendix 7.4.3 Extraintestinal manifestations (baseline and changes after drug initiation)

Appendix 7.5 Prior and concomitant medication

Appendix 7.6.1 Simple clinical colitis activity index, Mayo score and physician global assessment at baseline at week 52 and 78

Appendix 7.6.2 Mayo endoscopic subscore at baseline and > 8 weeks

Appendix 7.6.3 Colectomy, IBD-hospitalizations, and corticosteroid use within 52 weeks

Appendix 7.7 Adverse Events (serious and non-serious AEs)

Appendix 7.8 Laboratory results (CRP, Fecal Calprotectin, Serum albumin)

Appendix 7.2 Protocol Deviations

Not applicable

Appendix 8. ADDITIONAL DOCUMENTS

Not applicable.

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-Aminosalicylate
AE	Adverse Event
AEM	Adverse Event Monitoring
BMI	Body Mass Index
CRP	C-Reactive Protein
DCT	Data Collection Tools
EU	European Union
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
IBD	Inflammatory Bowel Disease
IEC	Independent Ethics Committee
IQR	Interquartile Range
IRB	Institutional Review Board
MGB	Mass General Brigham
NIS	Non-Interventional Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PGA	Physician Global Assessment
RPDR	Research Patient Data Registry
SCCAI	Simple Clinical Colitis Activity Index
SD	Standard Deviation

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Abbreviation	Definition
SFCR	Steroid-Free Clinical Remission
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
USA	United States of America
YRR	Your Reporting Responsibilities

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Redacted	Redacted	Redacted	Redacted
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4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) Approval of Protocol	7 September 2021	NA	Protocol was exempt from IRB approval.
Start of Data Collection	01 March 2022	24 February 2022	
End of Data Collection	30 April 2022	30 April 2022	
Registration in the EU PAS Register	NA	28 February 2022	
Final Report of Study Results	30 March 2023	19 November 2022	

6. RATIONALE AND BACKGROUND

Tofacitinib is an oral Janus kinase inhibitor that was approved for the treatment of moderate-to-severe UC in 2018. The Phase 3 OCTAVE clinical trials demonstrated the efficacy of induction and maintenance tofacitinib compared to placebo in this population.[1] A recent long-term extension study of OCTAVE open demonstrated that nearly 60% of patients who were in remission at baseline and 34% of all other patients maintained or achieve remission after 36 months of tofacitinib therapy.[2] However, data related to clinical trials may be less reflective of real-world clinical practice due to the strict exclusion criteria in such studies. Real-world outcomes of tofacitinib therapy in UC are currently limited.[3-7] A recent prospective Dutch cohort of 123 UC patients with prior failure of anti-tumor necrosis factor (TNF) and vedolizumab therapies identified a clinical remission rate of 27% at a median of 24 weeks after initiation of tofacitinib therapy and a 6% rate of adverse events (AEs) requiring therapy discontinuation.[6] Real-world outcomes of tofacitinib therapy at 52 weeks and beyond are nevertheless lacking. Therefore, the aim is to perform a retrospective cohort study to assess long-term clinical outcomes at 52 and 78 weeks of tofacitinib therapy for UC.

This non-interventional study is designated as a post-authorization safety study (PASS) and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

This retrospective cohort study assessed real-world clinical outcomes at 12 and 18 months after initiation of tofacitinib therapy for ulcerative colitis.

Primary objective:

1. Assess proportions of clinical remission (Simple Clinical Colitis Activity Index [SCCAI] or Mayo <2 or physician global assessment [PGA]) and corticosteroid-free clinical remission (with no use of corticosteroids within 30 days preceding assessment) at Week 52 and 78 after tofacitinib induction in a real-world cohort of patients with UC.

Secondary objectives:

1. Use univariable and multivariable logistic regression to identify baseline predictors of corticosteroid-free clinical remission (with no use of corticosteroids within 30 days preceding assessment) at Weeks 52 and 78.

2. Use multivariable cox regression to identify baseline predictors of drug survival (ie, time to tofacitinib discontinuation or colectomy due to refractory disease activity).

3. Assess proportions of endoscopic response (ie, decrease in Mayo endoscopic subscore by 1 point) and endoscopic remission (Mayo endoscopic subscore <1) >8 weeks post tofacitinib induction.

4. Assess proportions of biochemical response (improvement in C-reactive protein (CRP) or calprotectin by >25% or normalization) and remission (normalization of CRP or calprotectin) at Weeks 8, 26, 52, and 78.

5. Describe proportions of dose de-escalation (10 to 5 mg) or dose re-escalation (5 to 10 mg) at any point during follow-up. Median times to dose changes will be reported.

6. Assess proportions of clinical remission and corticosteroid-free remission 8-16 weeks after does de-escalation and dose re-escalation.

7. Describe proportions of colectomy, inflammatory bowel disease (IBD)-related hospitalization (ie, UC listed as primary or secondary discharge diagnosis), and corticosteroid use within 52 weeks of tofacitinib induction.

8. Assess proportions of patient-reported improvement in articular extraintestinal manifestations at 52 weeks after tofacitinib induction (among those with articular manifestations at baseline).

9. Assess proportions of all possible complications (eg, infection, thromboembolism, shingles, new malignancy) that are documented during available follow-up.

10. Describe reasons for treatment discontinuation.

8. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1 substantial	16 March 2022	6. Milestones	Updated start of milestones to actual date	Administrative
		9.1 Study Design 9.2 Setting 9.2.1 Inclusion criteria	Changed the start date of time window to collect data from 01 October 2018 to 01 May 2018.	Extension data collection time window in order to increase eligible study population and correspond to launch of tofacitinib in UC.
2 administrative	06 June 2022	6. Milestones	Study planned milestones were updated.	Milestones were aligned with sponsor internal CCTR planned dates.
		8. Research questions and objectives	Addition of one exploratory objective.	An additional time point was added at 12 weeks as exploratory objective, because most patients have data available at that time point.
		9.1 Study Design	Corrected the date of last data corrected from 01 January 2022 to 01 April 2022. Added exploratory endpoint.	Corrected the date of last data corrected from 01 January 2022 to 01 April 2022. This was a wrongly written by mistake. Coherent with the updates in research objects, the exploratory endpoint was added to this section.
		9.2 Settings	Corrected the date of last data corrected from 01 January 2022 to 01 April 2022.	Corrected the date of last data corrected from 01 January 2022 to 01 April 2022. This was a wrongly written by mistake.
		9.7 Data analysis and tables	Added exploratory endpoint to data analysis.	Coherent with the updates in research objects, the exploratory endpoint was added to this section.
		Annex 1 List of stand-alone documents	Updated the date of the new abstract.	Updated the date of the new abstract.

9. RESEARCH METHODS

9.1. Study Design

This is a retrospective cohort study of patients aged >18 years with UC who initiate tofacitinib therapy after 01 May 2018 (month of Food and Drug Administration [FDA] approval) in the Mass General Brigham (MGB) health system. Patients were followed from the time of tofacitinib initiation to tofacitinib discontinuation, total colectomy, or the last available gastroenterology encounter through 01 April 2022. Independent variables were recorded as the most recent values available within 3 months prior to tofacitinib initiation. Primary endpoint was proportion of patients in clinical remission and corticosteroid-free clinical remission at Weeks 52 and 78, and secondary endpoints were clinical remission, drug survival (ie, treatment persistence), endoscopic response/remission, and biochemical response/remission.

9.2. Setting

The study setting is the MGB health system, which includes Brigham and Women's Hospital, Brigham and Women's Faulkner Hospital, Massachusetts General Hospital, Newton-Wellesley Hospital, McLean Hospital, and North Shore Medical Center in Massachusetts, United States of America (USA). Adult patients were included if they initiated tofacitinib therapy for UC on or after 01 May 2018. Patient medical record numbers were identified using these search criteria in the MGB Research Patient Data Registry (RPDR) and thereafter Epic electronic health records were manually reviewed for clinical data. Patients were followed from the time of tofacitinib initiation to tofacitinib discontinuation, total colectomy, or the last available gastroenterology encounter through 01 April 2022.

9.3. Subjects

9.3.1. Inclusion Criteria

Participants must have met all of the following inclusion criteria to be eligible for inclusion in the study:

1. Age of 18 years or older.
2. Initiation of tofacitinib therapy for ulcerative colitis on or after 01 May 2018.
3. Patient within the MGB health system.

9.3.2. Exclusion Criteria

Participants meeting any of the following criteria were not included in the study:

1. History of prior colectomy.
2. Primary indication of tofacitinib therapy is not ulcerative colitis.

3. Diagnosis of Crohn's disease or indeterminate colitis.

4. Combination biologic therapy (eg, tofacitinib and vedolizumab simultaneously).

9.4. Variables

Independent variables abstracted were baseline characteristics present at the time of tofacitinib initiation (or most recent available values within 3 months of tofacitinib initiation). These will include but will not be limited to:

Variable	Role	Data source(s)	Operational definition
Age	Baseline characteristic	Mass General Brigham Research Patient Data Registry	Demographics
Sex	Baseline characteristic	Mass General Brigham Research Patient Data Registry	Demographics
Race/ethnicity	Baseline characteristic	Mass General Brigham Research Patient Data Registry	Demographics
Body mass index (BMI)	Baseline characteristic	Mass General Brigham Research Patient Data Registry	Demographics
UC duration (years)	Baseline characteristic	Mass General Brigham Research Patient Data Registry	Disease characteristics
Montreal disease extent	Baseline characteristic	Mass General Brigham Research Patient Data Registry	Disease characteristics
Mayo endoscopic severity score and histologic activity (based on last colonoscopy)	Baseline characteristic/Outcome	Mass General Brigham Research Patient Data Registry	Secondary endpoint
Mayo or SCCAI as documented in clinic notes	Baseline characteristic/Outcome	Mass General Brigham Research Patient Data Registry	Primary endpoint
Physician global assessment (PGA)	Baseline characteristic/Outcome	Mass General Brigham Research Patient Data Registry	Primary endpoint
Daily bowel movement frequency	Baseline characteristic/Outcome	Mass General Brigham Research Patient Data Registry	Disease characteristics
C-reactive protein	Baseline characteristic/Outcome	Mass General Brigham Research Patient Data Registry	Secondary endpoint
Serum albumin	Baseline characteristic/Outcome	Mass General Brigham Research Patient Data Registry	Confounder
Fecal calprotectin	Baseline characteristic/Outcome	Mass General Brigham Research Patient Data Registry	Secondary endpoint
Concomitant UC medications (corticosteroids [budesonide, prednisone, methylprednisolone], 5-ASA, azathioprine,	Exposure	Mass General Brigham Research Patient Data Registry	Concomitant medication

Variable	Role	Data source(s)	Operational definition
6-mercaptopurine, methotrexate, biologic therapies)			
Prior UC medications (5-ASA, azathioprine, 6-mercaptopurine, methotrexate, biologic therapies)	Exposure	Mass General Brigham Research Patient Data Registry	Prior Medication
Substance use (current cannabis, current opioids)	Exposure, Baseline characteristics	Mass General Brigham Research Patient Data Registry	Demographics
Smoking (current, former, or never)	Exposure, Baseline characteristics	Mass General Brigham Research Patient Data Registry	Demographics
History of malignancy	Baseline characteristics	Mass General Brigham Research Patient Data Registry	Disease characteristics
UC-related hospitalization within the last 12 months	Baseline characteristics	Mass General Brigham Research Patient Data Registry	Disease characteristics
History of Colectomy (if applicable)	Baseline characteristics	Mass General Brigham Research Patient Data Registry	Disease characteristics
Extraintestinal manifestation (presence at drug initiation and improvement after drug initiation)	Baseline characteristics/outcome	Mass General Brigham Research Patient Data Registry	Disease characteristics/secondary endpoint
Adverse events (AEs)	Outcome	Mass General Brigham Research Patient Data Registry	Safety Data/Secondary endpoint
Tofacitinib intake (initiation date, dose taken and any change of dosage, discontinuation)	Exposure/Outcome	Mass General Brigham Research Patient Data Registry	NA

9.5. Data Sources and Measurement

The primary data source was Epic electronic health records, and the majority of data was collected via manual chart review. Medical record numbers and demographic variables (sex, race/ethnicity) were obtained from the MGB RPDR using the pre-specified inclusion/exclusion criteria.

9.6. Bias

The study population includes referral patients at a tertiary center. Therefore, results may be biased towards individuals with more complex disease and may not reflect the general UC population in the United States. This is an inherent limitation to the study.

9.7. Study Size

The estimated sample size was 100 patients per the MGB RPDR. Among these, approximately 85 patients were estimated to have 12 or more months of follow-up. The primary objective is to describe the proportion of patients in clinical remission and corticosteroid-free clinical remission at 52 and 78 weeks, and for this p-values are not calculated (similarly, a power calculation is not relevant for the primary outcomes). We hypothesized, based on prior data, that approximately 40% or more of patients would be in corticosteroid-free clinical remission at these timepoints.

9.8. Data Transformation

Data were manually abstracted from Epic electronic medical records and collected using a Microsoft Excel template (this will serve as the Data Collection Tool), which were stored on a MGB computer and MGB Dropbox (cloud software). The excel file is password protected.

No data transformations or calculations were performed beyond those described in the statistical methods (below).

9.9. Statistical Methods

De-identified data was imported into Stata/SE 17 for statistical analysis.

9.9.1. Main Summary Measures

Descriptive statistics were presented to describe patient characteristics. Categorical covariates were described by frequency distribution while continuous covariates expressed in terms of their mean and standard deviation or median and interquartile range (IQR) as appropriate.

9.9.2. Main Statistical Methods

Univariate and multivariable logistic regression models were used to identify predictors (among all independent variables) of corticosteroid-free remission at Week 52 and week 78 (2 separate models). Variables from the univariable analysis that were statistically significant at $p<0.05$ were included in the final multivariable model. Adjusted odds ratios with 95% confidence intervals were calculated using logistic regression models and reported in the final models. All analyses above were also completed at 12 weeks (in addition to 52 and 78 weeks) as an exploratory endpoint.

A Kaplan-Meier curve showing the survival function (ie, time to drug discontinuation for non-response) of tofacitinib therapy was generated. Univariable and multivariable Cox proportional hazards modeling were used to identify predictors (among all independent variables) of tofacitinib drug survival. Variables on univariable analysis associated with drug survival at $p<0.05$ were included in the final multivariable model. Patients were censored at time of colectomy, treatment discontinuation, death, or loss to follow-up. The proportional hazards assumption was tested using Schoenfeld residuals. Adjusted hazard ratios with

95% confidence intervals were reported in the final model. Stata/SE 17 was used for all analyses.

9.9.3. Missing Values

Patients with missing data for any independent variables were excluded from multivariable analyses.

9.9.4. Sensitivity Analyses

Because age and BMI were found to be significant predictors and they are both continuous variables, a quadratic relationship for each of these two variables was examined in the multivariable logistic regression model for SFCR78 using both a linear and squared term.

9.9.5. Amendments to the Statistical Analysis Plan

None

9.10. Quality Control

Data abstracted from electronic medical records were reviewed by 2 study investigators to ensure accuracy. The statistical analysis was completed by 1 study investigator and reviewed separately by a second investigator.

9.11. Protection of Human Subjects

Subject information and consent

Not applicable.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The study protocol was submitted to the IRB and received an exemption from IRB approval.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP).

10. RESULTS

10.1. Participants

The cohort included 73 patients who initiated tofacitinib for UC with a median follow-up of 88 weeks (IQR 40.9-151.0 weeks).

10.2. Descriptive data

Among 73 patients, 60.2% were female, 54.7% had prior exposure to ≥2 anti-tumor necrosis factor agents, 74.0% had prior exposure to vedolizumab, and 54.7% were receiving concomitant oral or IV corticosteroids at the time of tofacitinib initiation. Other baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics

Characteristic	Value
N	73
Female	44 (60%)
Male	29 (40%)
Age, y, median (IQR)	41.2 (28.1, 54.0)
UC duration, y, median (IQR)	9.5 (4.4, 15.5)
Race	
Caucasian	67 (92%)
Black	0 (0%)
Asian	4 (5%)
Other/Unknown	2 (3%)
Hispanic	0 (0%)
Number of prior anti-TNFs	
0	4 (5%)
1	29 (40%)
2	29 (40%)
3	10 (14%)
4	1 (1%)
Prior ustekinumab	8 (11%)
Prior vedolizumab	54 (74%)
Prior 5-ASA	71 (97%)
Current 5-ASA	12 (16%)
Prior immunomodulator	54 (74%)
Current immunomodulator	6 (8%)
Current steroids	40 (55%)
Prednisone/methylprednisolone	33 (45%)
Budesonide	7 (10%)
Current oral contraceptive	6 (8%)
Hypertension	19 (26%)
Hyperlipidemia	13 (18%)
Diabetes	7 (10%)
History of coronary artery disease	5 (7%)

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Characteristic	Value
History of cerebrovascular accident	1 (1%)
BMI, median (IQR)	25.6 (21.6, 28.9)
Arthralgia at time of initiation	27 (37%)
Endoscopic extent >E1 (i.e. >proctitis)	62 (85%)
Endoscopic severity	
None	6 (8%)
Mild	9 (12%)
Moderate	38 (52%)
Severe	20 (27%)
Smoking	
Never	59 (81%)
Current	2 (3%)
Former	12 (16%)
Current cannabis use	11 (15%)
Current opioid use	7 (10%)
UC hospitalization within 12 months	19 (26%)
Serum albumin, g/dL, median (IQR)	4.1 (3.8, 4.3)
CRP, mg/L, median (IQR)	5.1 (1.7, 16.7)
Fecal calprotectin > 120 ug/g	27 (90%)
SCCAI, median (IQR)	5 (3, 8)
Daily bowel movement frequency, median (IQR)	6 (3.5, 10)

Albumin, C-reactive protein, fecal calprotectin, SCCAI, and bowel movements were the most recent values available within 3 months prior to drug initiation. The most recent endoscopic data preceding tofacitinib initiation was used: median 19.1 weeks (IQR 6.1-46.1 weeks) prior to tofacitinib initiation. Abbreviations: IQR = interquartile range, TNF= tumor necrosis factor, ASA = aminosalicylic acid, CRP = C-reactive protein, SCCAI = simple clinical colitis activity index.

10.3. Outcome Data

Among patients with sufficient follow-up data, 39/71 (54.9%), 40/69 (58.0%), and 31/60 (51.7%) achieved SFCR at 12, 52, and 78 weeks, respectively. Among 60 patients with at least 78 weeks of follow-up, 20 (33.3%) had sustained SFCR at 12, 52, and 78 weeks. Among 27 patients with baseline steroid use and at least 78 weeks of follow-up, 14 achieved SFCR at 78 weeks (51.9%). Endoscopic response and remission were achieved in 39/47 (83.0%) and 21/47 (44.7%), respectively. Median time to endoscopy was 58.1 weeks (IQR 30.7-103.6 weeks) after tofacitinib initiation. Other outcomes are presented in Table 2.

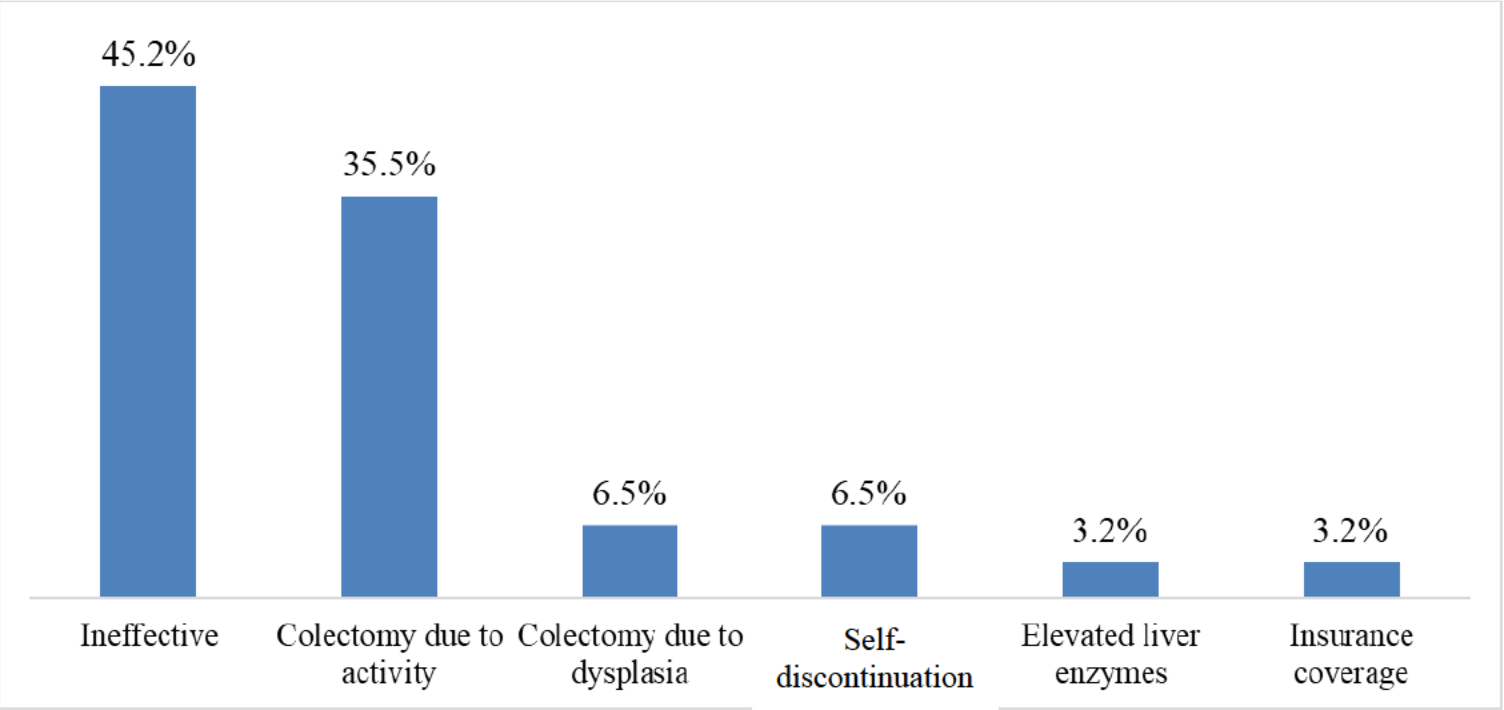
Tofacitinib was discontinued among 31/73 (42.5%) patients during follow-up. Discontinuation specifically due to non-response or colectomy for refractory disease occurred in 25/73 (34.2%) after a median of 27.7 weeks (interquartile range [IQR] 13.0-44.3 weeks). Other reasons for discontinuation were colectomy for dysplasia (n=2), non-adherence (n=2), insurance coverage (n=1), and an AE (elevated liver enzymes, n=1) (Figure 1).

Table 2. Unadjusted Outcomes

Outcomes	Tofacitinib
Clinical remission 12 weeks, fraction (%)	40/71 (56%)
Steroid-free clinical remission 12 weeks, fraction (%)	39/71 (55%)
Clinical remission 52 weeks, fraction (%)	44/69 (64%)
Steroid-free clinical remission 52 weeks, fraction (%)	40/69 (58%)
Clinical remission 78 weeks, fraction (%)	35/60 (58%)
Steroid-free clinical remission 78 weeks, fraction (%)	31/60 (52%)
Endoscopic response, fraction (%)	40/48 (83%)
Endoscopic remission, fraction (%)	22/48 (46%)
Biochemical response, fraction (%)	23/30 (77%)
Improvement in articular extraintestinal manifestation, fraction (%)	13/23 (57%)
Colectomy, fraction (%)	14/73 (19%)
Adverse event, fraction (%)	15/73 (21%)
Dose de-escalation, fraction (%)	38/73 (52%)
UC-related hospitalization	3/73 (4%)
Treatment discontinuation during follow-up	31/73 (43%)
Treatment discontinuation due to adverse event	1/73 (1%)

Denominators vary due to missing data and variable follow-up time.

Figure 1. Reasons for Treatment Discontinuation During Follow-up



Percentages are among n=31 patients who discontinued treatment during follow-up.

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10.4. Main Results

SFCR Week 52 logistic regression analysis

Univariable logistic regression identified a significant, positive association between older age (OR 1.05, 95% CI 1.01-1.08) and SFCR at 52 weeks. No other factors at $p<0.05$ were identified and therefore no additional covariates were included in the multivariable model. (Table 3).

SFCR Week 78 logistic regression analysis

Univariable logistic regression identified significant, positive associations between older age (OR 1.06, 95% CI 1.02-1.10) and higher BMI (OR 1.21, 95% CI 1.07-1.38) with SFCR 78. On multivariable analysis, older age and higher BMI were again positively associated with SFCR 78 (age at initiation: OR 1.04, 95% CI 1.00-1.09; BMI: OR 1.17, 95% CI 1.02-1.33) (Table 3). Because age and BMI are continuous variables, we examined a quadratic relationship for each using both a linear and squared term. There was no association between $(BMI)^2$ (OR 1.00, 95% CI 0.98-1.00) or $(Age\ at\ initiation)^2$ (OR 1.00, 95% CI 1.00-1.00) with SFCR 78, suggesting that both previously observed associations were linear.

Table 3. Multivariable Logistic Regression Models

Covariate(s) for SFCR Week 52	OR	95% LCL	95% UCL	P-value
Age at initiation	1.05	1.01	1.08	0.01
Covariate(s) for SFCR Week 78				
Age at initiation	1.04	1.00	1.09	0.04
BMI	1.17	1.02	1.33	0.02

Abbreviations: SFCR = steroid-free clinical remission, OR = odds ratio, LCL = lower confidence limit, UCL = upper confidence limit.

Tofacitinib drug survival analysis

Kaplan-Meier analysis of tofacitinib drug survival is presented in Figure 2. Univariable Cox regression identified associations between age at initiation (HR 0.92, 95% 0.89-0.96), UC duration (HR 0.92, 95% CI 0.86-0.99), BMI (HR 0.87, 95% CI 0.79-0.95), UC hospitalization within last 12 months (HR 2.40, 95% CI 1.05-5.50), and SCCAI (HR 1.18, 95% CI 1.06-1.31) with tofacitinib drug survival. On multivariable analysis, only the association of age at initiation persisted (HR 0.94, 95% CI 0.91-0.98) (Table 4). For Cox analyses, the proportional hazards assumption was confirmed using Schoenfeld residuals.

Figure 2. Kaplan-Meier Analysis of Time to Tofacitinib Discontinuation Due to Non-response

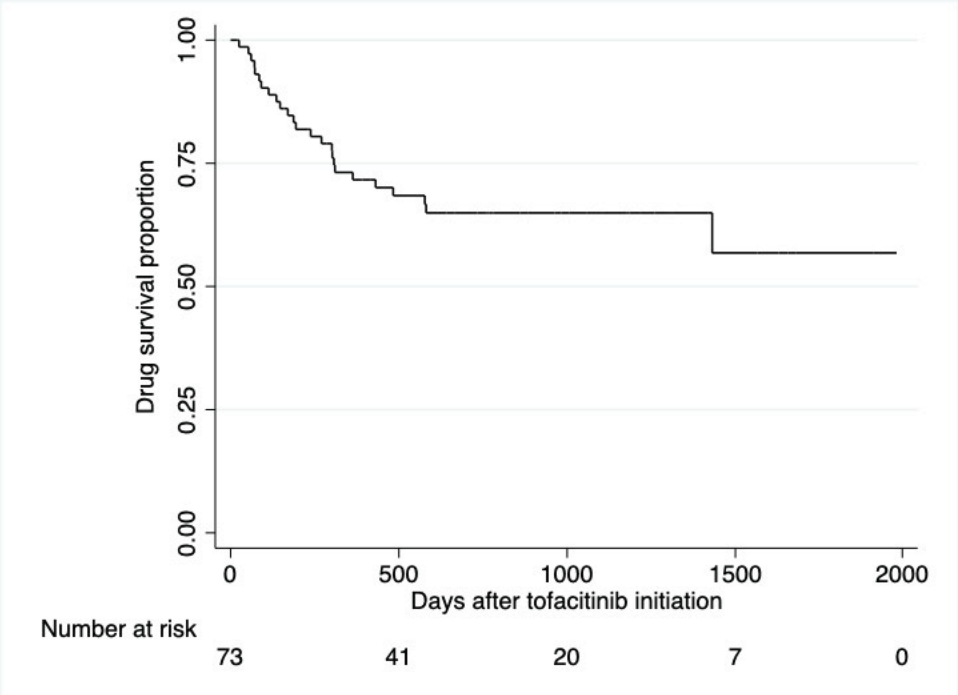

Table 4. Cox Model for Tofacitinib Drug Survival

Covariate	HR	95% LCL	95% UCL	P-value
Age at initiation	0.95	0.92	0.99	0.01
UC duration	0.95	0.88	1.02	0.15
BMI	0.92	0.83	1.01	0.09
UC hospitalization within last 12 months	1.60	0.61	4.21	0.34
SCCAI	1.09	0.98	1.21	0.11

Abbreviations: SFCR = steroid-free clinical remission, OR = odds ratio, LCL = lower confidence limit, UCL = upper confidence limit, SCCAI = simple clinical colitis activity index.

10.5. Other Analyses

Dose de-escalation outcomes

Dose de-escalation from 10 mg twice daily dosing occurred among 38/73 (52.1%) patients to 10 or 11 mg (n=35) or 15 mg (n=3) total daily dosing after a median of 36.9 weeks (IQR 20.6-62.3 weeks) from tofacitinib initiation. All patients were in SFCR prior to dose de-escalation. Among these 38 patients, 34 had at least 52 weeks of follow-up, 2 of whom discontinued tofacitinib for reasons unrelated to treatment efficacy (dysplasia requiring

colectomy and elevated liver enzymes). Among the remaining 32 patients, 18 (56.3%) were in SFCR at 52 weeks after dose de-escalation. Of the remaining 14 patients, 12 were re_escalated to 10 mg twice daily dosing and 2 discontinued therapy due to loss of response.

Data on dose re-escalation were not available prior to 1 April 2022 (end of study period).

Subgroup analysis
Among patients with prior anti-TNF and vedolizumab failure, proportions of patients achieving SFCR 12, 52, and 78 with tofacitinib were 26/50 (52.0%), 26/49 (53.1%), and 21/44 (47.7%), respectively.

10.6. Adverse Events/Adverse Reactions

There was 1 AE attributed to tofacitinib therapy, which was elevated liver enzymes. This patient discontinued tofacitinib due to the AE.

There were also 2 reported "possible miscarriages," one of which was associated with a positive beta HCG followed by a negative beta HCG 3 days later. The second involved a patient who reported observation of a miscarriage but there was no laboratory or other objective documentation to confirm pregnancy. Neither patient intended to become pregnant and neither discontinued tofacitinib due to these events.

11. DISCUSSION

11.1. Key Results

In this refractory UC population, tofacitinib treatment was effective in achieving SFCR at 78 weeks for >50% of patients with only 34% discontinuing treatment due to non-response during follow-up. Proportions of patients achieving SFCR were similar even among those with prior anti-TNF and vedolizumab failure. We also observed endoscopic remission in 45% of patients after a median of 58 weeks of therapy. Tofacitinib was found to be well-tolerated, as only one patient discontinued treatment due to an AE (elevated liver enzymes). No new safety risks were identified in this cohort compared to previous data.[1]

11.2. Limitations

Limitations include the retrospective design, potential omissions and errors in clinical documentation, variable follow-up times, inability to detect adverse events that may have occurred outside of our tertiary health care center, and sample size limitations that precluded additional subgroup analyses. Our primary analysis also depends on physician documentation of SCCAI scores or global assessments, which are subjective and may vary by IBD provider. We therefore included an analysis on drug survival, which is a more objective assessment of the durability of tofacitinib treatment. While our study also provides more endoscopic outcome data compared to other real-world cohort studies,[2-5] the sample size is likely insufficient to make conclusions about the effectiveness of tofacitinib to achieve and maintain deep remission in UC.

11.3. Interpretation

Our multivariable analyses found that patients of older age had greater odds of SFCR 78 as well as greater drug survival. At least two prior studies have reported favorable outcomes for older adults receiving tofacitinib for UC.[2,6] In a post-hoc analysis of the OCTAVE Sustain study, age, among other factors, was positively associated with a higher odd of clinical remission at week 52 in a multivariable model.[6] A multi-center study in the United Kingdom found a positive, independent association between younger age and primary non-response to tofacitinib.[2] However, there was also a correlation between age and disease duration and severity? In our study, there was a significant association between disease duration and drug survival on univariable analysis which was attenuated in the multivariable model including age. Therefore, it is possible that older age is the driver of this association, which may represent later-onset UC patients who are known to have a less severe disease course.[7] While tofacitinib may be more effective in older adults, the decision to treat must be balanced with consideration of AEs, which occurred more commonly among adults >50 years of age.

We also identified an independent and positive association between higher BMI and SFCR 78. There are limited data regarding BMI and clinical outcomes with tofacitinib therapy. A post-hoc analysis of OCTAVE did not identify an association between BMI and clinical remission of UC.[8] BMI also was not associated with tofacitinib efficacy in studies using pooled clinical trial data for both rheumatoid arthritis and psoriatic arthritis.[9,10] We hypothesize that a higher BMI may reflect a more nutritionally replete status and therefore less severe disease that may be more responsive to treatment.

Our study provides important real-world data regarding dose de-escalation of tofacitinib after achieving SFCR on standard dosing. More than 50% of patients in our cohort who underwent dose de-escalation remained in SFCR after 52 weeks of follow-up. Less than 40% of those de-escalated required re-escalation. Likewise, OCTAVE Open identified a sustained remission rate of 75% at 52 weeks after dose de-escalation.[11] Similar results were found in an RCT of 140 patients at month 6 after de-escalation.[12] In one real-world study, only one third of patients had recurrence of symptoms after de-escalation to 10 mg total daily dosing, after which dose escalation re-captured response in nearly 50% of patients.[2] In combination, these findings support attempting dose de-escalation for patients who achieve SFCR on 10 mg twice daily dosing to limit the risk of potential AEs.

11.4. Generalizability

The study was conducted in an urban, tertiary referral center. The majority of patients were also Caucasian. Therefore the results of this study may not be generalizable to other settings and populations of different demographic compositions.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

In summary, tofacitinib appears to be an effective and durable treatment for UC through 78 weeks of follow-up in a largely bio-exposed population, including a subgroup that was exposed to both anti-TNF agents and vedolizumab. Remission appears to be maintained for the majority of patients who undergo dose de-escalation and adverse events are similar to those previously reported. Patients of older age and higher BMI may have better response to tofacitinib therapy. As the treatment algorithms for UC grow in complexity, there is a rising need for both head-to-head clinical trials and real-world comparative effectiveness studies to determine the most appropriate positioning of tofacitinib in this population.

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15. LIST OF SOURCE TABLES AND FIGURES

All tables and figures are included in the body of the study report.

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