NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study Information

Title	Real World Evidence of the Usage of Tofacitinib in Ulcerative Colitis Patients in Lebanon
Protocol Number	A3921393
Version Identifier of the Final Study Report	Version 1.0
Date	11 January 2023
EU Post Authorization Study (PAS) Register Number	EUPAS38515
Active Substance	ATC: L04AA29
Medicinal Product	Tofacitinib
Research Question and Objectives	To describe the effectiveness of tofacitinib in patients with ulcerative colitis in a Lebanese cohort Primary objectives: • To evaluate the real-world (RW) effectiveness of tofacitinib in ulcerative colitis patients by improvement in the proportion of patients achieving clinical remission and proportion of patients achieving endoscopic remission and response. Secondary Objectives: • To further evaluate the RW effect of tofacitinib treatment including proportion of patients that are still on tofacitinib treatment, the proportion of patients

	undergoing inflammatory bowel disease (IBD) surgery, and lab parameters change from baseline.
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Annex 1. List of stand-alone documents

Not applicable.

Not applicable.

Not applicable.

Not applicable.

Not applicable.

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
AUBMC	American University of Beirut Medical Center
CD	Crohn's Disease
COOP	Cooperative of Government Employees
CRF	Case Report Form
CRP	C-Reactive Protein
EU	European Union
FDA	Federal Drug Administration
HZV	Herpes Zoster Virus
IBD	Inflammatory Bowel Disease
ICMJE	International Committee of Medical Journal Editors
JAK	Janus Kinase
LDL	Low-Density Lipoprotein
NI	Non-Interventional
NIS	Non-Interventional Study
NSSF	National Social Security Fund
PAS	Post-Authorisation Safety
PASS	Post-Authorisation Safety Study
RCT	Randomized Controlled Trials
RW	Real world

Abbreviation	Definition
RWD	Real World Data
SAP	Statistical Analysis Plan
SPSS	Statistical Package for Social Sciences
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
YRR	Your Reporting Responsibilities

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

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

Not applicable.

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5. MILESTONES

Milestone	Planned Date	Actual Date	Comments
Registration in the European (EU) PAS Register	17 May 2021	24 November 2021	
Start of Data Collection	30 November 2021	30 November 2021	
End of Data Collection	30 April 2022	29 April 2022	
Final Study Report	30 March 2023	11 January 2023	

6. RATIONALE AND BACKGROUND

Ulcerative Colitis is a chronic inflammatory bowel disease with a relapsing-remitting pattern that causes an increased frequency of bowel movements and bloody diarrhea, leading to organ damage and impaired quality of life.[1] The primary goals of therapy in ulcerative colitis (UC) are reducing the mucosal inflammation and maintaining symptom remission, though these aims are not achieved in all patients.[1] Despite the array of medical options available, treatment failure is common and refractory disease represents an unmet clinical need.[2] Hence, additional treatments including those with different new modes/mechanisms of actions are needed.

Tofacitinib, an inhibitor of the Janus Kinase (JAK) family of kinases, was approved in Lebanon in August 2018 at a dose of 5 mg or 10 mg twice daily for the treatment of adults with moderate-to-severe UC, who have had an inadequate response or who are intolerant to tumor necrosis factor (TNF) blockers. The efficacy profile and safety profile of tofacitinib have been demonstrated as induction and maintenance therapy in 3 Phase 3, randomized, placebo-controlled trials in patients with moderate to severe ulcerative colitis.[2] However, the study design and procedures in the previous randomized controlled trials (RCT) may not always reflect the clinical practice. It is important to clinicians, patients, and payers to ascertain the outcomes in the Lebanese environment where the drug is used.

Real world data has become increasingly important in providing additional evidence of treatment effectiveness in clinical practice. Real world data (RWD) on the use of tofacitinib in ulcerative colitis had not been reported previously in Lebanon, where is the need to conduct this study. The use of observational clinical data collected from the patients during regular treatment visits will allow for the generation of data on the induction, maintenance, and long-term effectiveness of tofacitinib in Lebanon outside the confines of the RCT.

This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and was conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study was to describe the effectiveness of tofacitinib in the treatment of ulcerative colitis in a Lebanese cohort:

Primary Objectives:

- To evaluate the real-world (RW) effectiveness of tofacitinib in ulcerative colitis patients by improving the proportion of patients achieving clinical remission and proportion of patients achieving endoscopic remission and response.

Secondary Objectives:

- To further evaluate the RW effect of tofacitinib treatment including proportion of patients that are still on tofacitinib treatment, proportion of patients undergoing IBD surgery, and lab parameters changes from baseline.

8. AMENDMENTS AND UPDATES

Table 1 Amendments to the Protocol

Amendment Number	Date	Substantial or administrative amendment	Protocol Section(s) Changed	Summary of Amendment	Reason
1	29 Apr 2022	Administrative	3. Responsible Parties	Added an additional responsible researcher.	A new researcher was added to the study team.
			6. Milestones	Updated planned study milestones	Planned milestones were updated to be aligned with sponsor internal systems.
			9.1 Study design and 9.5 Study size	The number of estimated patients was corrected.	The number of estimated patients was adjusted to an updated review of the database.
			Annex 1 List of stand-alone documents	Updated abstract information.	The abstract was updated and the information in the annex was changed accordingly.
2	11 Jan 2023	Administrative	Title Page and section 3. Responsible parties	Updated the job title and address of the NI study lead	Administrative

9. RESEARCH METHODS

9.1. Study Design

This is an observational retrospective cohort study that describes the effectiveness of tofacitinib for the treatment of patients with ulcerative colitis in Lebanon. Data of patients meeting the inclusion criteria will be extracted from the database of the American University of Beirut Medical Center (AUBMC). It is estimated that data of about 60 patients who have received treatment with tofacitinib for UC in Lebanon, with minimal follow-up period of 12 weeks will be included.

Primary Endpoints:

- Proportion of patients achieving clinical remission*by 8 weeks, 26 weeks, and 52 weeks.
- Proportion of patients achieving endoscopic remission* and response* in ulcerative colitis as determined by the endoscopic Mayo score at 24 weeks.

Secondary Endpoints:

- A proportion of patients that are still on tofacitinib treatment at 1 year.
- A proportion of patients requiring IBD surgery after 1 year of follow up.
- Changes in calprotectin at 12 weeks compared to baseline following treatment with tofacitinib.
- Changes in C-reactive protein (CRP) at 12 weeks compared to baseline following treatment with tofacitinib.
- Changes in hemoglobin at 12 weeks compared to baseline following treatment with tofacitinib.
- Changes in Low-density lipoprotein (LDL) at 12 weeks compared to baseline following treatment with tofacitinib.

**Clinical remission is defined as per reported by the treating physician, Endoscopic remission is defined as endoscopic Mayo score of 1 or 0, endoscopic response is defined as at least 1 grade improvement from baseline of endoscopic Mayo score.*

9.2. Setting

This study was a retrospective cohort study collecting data from patients with ulcerative colitis. The data were extracted from the database of the AUBMC, a university hospital in Beirut. The data collection occurred over a period of 5 months. The patients included were UC patients who started treatment on tofacitinib and fulfilled the inclusion and exclusion criteria below.

9.3. Subjects

9.3.1. Inclusion Criteria

Patients who met all the following inclusion criteria were eligible to participate in the study:

1. Male or female patients 18 years or older by the time of starting tofacitinib treatment
2. Confirmed diagnosis of ulcerative colitis.
3. Patients who have received treatment with tofacitinib for ulcerative Colitis with minimal follow-up period of 12 weeks.

9.3.2. Exclusion Criteria

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

1. Current or previous (within the last 2 years) indeterminate or not classified colitis.
2. Changing of IBD type (ie, from UC to Crohn's disease (CD), etc.) within the last 2 years.
3. Any combinations of tofacitinib with other advanced therapies.
4. Any previous use and discontinuation of tofacitinib.

9.3.3. Variables

Table 2 Endpoints Time Windows

Endpoint	Time Window
Clinical Remission at 8 weeks	8 weeks ±4 weeks
Clinical Remission at 26 weeks	26 weeks ±4 weeks
Clinical Remission at 52 weeks	52 weeks ±6 weeks
Endoscopic Remission at 24 weeks	24 weeks ±4 weeks
Endoscopic Response at 24 weeks	24 weeks ±4 weeks
Patients that are still on tofacitinib treatment at 1 year	52 weeks ±6 weeks
Patients requiring IBD surgery after 1 year of follow up	52 weeks ±6 weeks
Changes in CRP, calprotectin, hemoglobin, and LDL at 12 weeks compared to baseline following treatment with tofacitinib	12 weeks +8 weeks

Table 3. Variables

Variable	Role	Data Source(s)	Operational Definition
Age	Baseline Characteristics	AUBMC Database	Demographics, Medical History, and Concomitant/Prior Medication of Patients.
Gender			
Smoking Status			
Herpes Zoster Virus (HZV) Testing Prior to Tofacitinib Initiation			
Concomitant Medication			
Prior Medication			
Co-Morbidities			
Disease Characteristics			
Age at Diagnosis	Baseline Characteristics	AUBMC Database	Patient age in years at time of UC diagnosis.
Disease Extent			Ulcerative proctitis; left sided UC; extensive UC.
Extra Intestinal Manifestations of the Disease			Peripheral Arthropathy; Axial Involvement; Sweet Syndrome; Uveitis; Erythema Nodosum; Episcleritis; Scleritis; Pyoderma Gangrenosum; Oral Aphthous Ulcers; Primary Sclerosing Cholangitis; None
Tofacitinib Treatment			
Method of Dispensation of Tofacitinib	Baseline Characteristic	AUBMC Database	Ministry of Health; National Social Security Fund (NSSF); Cooperative of Government Employees (COOP); Armed Forces; Self-Payer
Tofacitinib Intake	Exposure	AUBMC Database	Dose; Duration of Treatment up to the Point of Data Extraction; Tofacitinib Dosage Adjustment following Induction
Medical Assessments			
Endoscopy	Primary Endpoint Component	AUBMC Database	Mayo Score at Initiation of Tofacitinib Therapy (0-12)
Laboratory	Secondary Endpoints	AUBMC Database	CRP (mg/L), Calprotectin (µg/mg), Hemoglobin (g/dl), LDL

Variable	Role	Data Source(s)	Operational Definition
			Cholesterol (mg/dl)
Safety			
Adverse Events (AE)	Exposure	AUBMC Database	Type of Adverse Events

9.4. Data Sources and Measurement

Data were extracted from the database at the AUBMC and entered into electronic case report form (CRF). The data does not contain personalized information. Data were collected on patient's demography, disease features, treatment history, lab parameters, clinical and endoscopic assessments before and after tofacitinib treatment, tofacitinib treatment withdrawal and adverse events.

9.5. Bias

This is a retrospective study including data of all patients in the AUBMC database who suffered from UC and were treated with tofacitinib for at least 6 weeks. As this is a non-hypothesis driven, predominantly descriptive study of the UC population in Lebanon, bias in this study is minimal.

9.6. Study Size

Based on the feasibility assessment, the number of patients on tofacitinib for ulcerative colitis in Lebanon was estimated to be 60. The study aimed to capture almost the entire population.

9.7. Data Transformation

All study data will be extracted from the database at the American university of Beirut medical center (AUBMC) and entered manually into an electronic case report form (CRF). The data does not contain personalized information. Entered data will be reviewed and compared to source data by another person to avoid data entry errors. There is no additional data that will be analysed for this study. All collected data were analyzed. Analysis was done by the Statistical Program for the Social Sciences (SPSS).

9.8. Statistical Methods

9.8.1. Main Summary Measures

All covariates were summarized to get information about frequency distribution and mean, median or standard deviation. When descriptive analysis of categorical data was performed, the numbers and percentages of patients in complete remission were presented for weeks 8, 26, and 52. When performing descriptive analysis on continuous data, means, medians, and standard deviations were provided for continuous variables.

9.8.2. Main Statistical Methods

The bivariate analysis was conducted to determine if there was any association between the outcome and the exposure (the covariates). Unadjusted comparisons of baseline characteristics for 8, 26, and 52 weeks after complete remission against outcome measures are provided. Appropriate tests were used based on the measure's distribution: Fisher's exact test provided proportions, 1 sample t-test provided means, and 1-sample Wilcoxon test provided medians; p-values were also generated. Time to treatment failure is described using Kaplan-Meier estimates, and the median time to event is presented along with the 25th and 75th percentiles of treatment failure. The odds ratio and proportional hazard are shown.

The safety of tofacitinib is described by the number and types of adverse events suffered by the patients.

9.8.3. Missing Values

Missing data was listed as missing. There was no imputation of missing data in this study.

9.8.4. Sensitivity Analyses

None.

9.8.5. Amendments to the Statistical Analysis Plan

None.

9.9. Quality Control

Data was entered manually into the CRF by medically qualified personnel. Entered data were reviewed and compared to source data by other personnel to avoid data entry errors.

9.10. PROTECTION OF HUMAN SUBJECTS

Subject information and consent

Not applicable

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

The final protocol was reviewed and approved by IRB(s) and/or IEC(s).

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 followed generally accepted research practices described in Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.

10. RESULTS

10.1. Participants

This is a retrospective cross-sectional national study conducted at the American University of Beirut Medical Center. Patients with ulcerative colitis (UC) who were treated with tofacitinib between 2018 and 2021 were included. A total of 60 patients were enrolled.

10.2. Descriptive Data

Table 4 shows the study patients baseline and disease characteristics. There were about the same number of female and male patients. The mean age was 34.5 years and the majority (58.3%) suffered for more than 5 years from ulcerative colitis. 58.3% of patients had received one or more biologics prior to tofacitinib. Only a minority of 8.3% did not take any other prior treatment. About one-third of patients stopped tofacitinib treatment within the follow-up period, primarily for lack of efficacy or loss of response.

Table 4 Demographic and disease characteristics

Variables	Categories	N (%)
Sex	Male	29 (48.3)
	Female	31 (51.7)
Mean age		34.5 ± 13.0
Smoking	Yes	14 (23.3)
	No	46 (76.7)
Duration of disease	2-5 years	24 (40.7)
	> 5 years	35 (58.3)
	Missing data	1 (1.7)
Mean years since diagnosis (n=59)		7.9 ± 4.7
Prior biologics	None	25 (41.7)
	1 biologic	18 (30.0)
	More than one biologic	17 (28.3)
Other prior treatment	None	5 (8.3)
	5 ASA	25 (41.7)
	Immunomodulator	5 (8.3)
	5 ASA and immunomodulator	25 (41.7)
Extra-intestinal manifestations	None	49 (81.7)
	Peripheral arthropathy	5 (8.3)
	Axial Involvement	1 (1.7)
	Pyoderma Gangrenosum	1 (1.7)
	Uveitis	1 (1.7)
	More than 1 manifestation	3 (5.0)
Disease extent	Ulcerative Proctitis	2 (3.3)
	Left Sided UC (Distal to Splenic Flexure)	21 (35.0)

Variables	Categories	N (%)
	Extensive (Proximal to Splenic Flexure)	37 (61.7)
HZV testing	Yes	27 (45.0)
	No	29 (48.3)
	Data unavailable	4 (6.7)
HZV result (n=27)	Positive	22 (81.5)
	Negative	5 (18.5)
Endoscopic mayo score at initiation	3	37 (61.7)
	2	20 (33.3)
	Data unavailable	3 (5.0)
Method of Dispensation	Ministry of Health	18 (30.0)
	NSSF	24 (40.0)
	Self-payer	18 (30.0)
Induction dose period in weeks	4	4 (6.7)
	8	40 (66.7)
	12	4 (6.7)
	More than 12	6 (10.0)
	Stayed on same dose as induction	6 (10.0)
First follow up clinical assessment (8 ± 4 weeks)	No response	5 (8.3)
	Clinical response	30 (50.0)
	Clinical remission	25 (41.7)
Second follow up clinical assessment (26 ± 4 weeks)	No response	9 (15.0)
	Clinical response	17 (28.3)
	Clinical remission	34 (56.7)
Third follow up clinical assessment (52 ± 6 weeks)	No response	3 (5.0)
	Clinical response	7 (11.7)
	Clinical remission	31 (51.7)
	Patient stopped treatment	14 (23.3)
	Patient to be followed	5 (8.3)
Endoscopic assessment (24 weeks ± 4)	No response	13 (21.7)
	Endoscopic response	5 (8.3)
	Endoscopic remission	28 (46.7)
	Patient to be followed	2 (3.3)
	Endoscopy not done/ insufficient data	12 (20.0)
Mayo score (n=48)	0 or 1	28 (58.3)
	2 or 3	20 (41.7)
Cessation of Tofacitinib	No	39 (65.0)

Variables	Categories	N (%)
	Yes	21 (35.0)
Mean duration of treatment in months (for those still on Tofacitinib) (n=39)		24.3 ± 9.5
Mean duration of treatment in months (for those who stopped tofacitinib) (n=21)		10.4 ± 6.1
For those who stopped, treatment after (n=21)	Ustekinumab	9 (42.9)
	Infliximab	5 (23.8)
	Adalimumab	3 (14.3)
	Vedolizumab	2 (9.5)
	Data unavailable	2 (9.5)

10.3. Main Results

Clinical remission was reported in 25, 34, and 31 patients (41.7%, 56.7%, and 51.7%) at 8, 26, and 52 weeks respectively (Table 5 - Table 7). Data was analyzed using the chi square test. When requirements were not met for the chi square test the Fisher exact test was used instead. P-values as a result of the Fisher's exact test are marked with a star in the tables.

The calculation of the odds ratio for clinical remission (Table 8) Using age, sex, duration of disease, disease extent, prior biologics use and reduction in CRP as variables, resulted in a significant effect for the latter two.

10.3.1. Patients Achieving Clinical Remission

Table 5 Proportion of Patients Achieving Clinical Remission by 8 Weeks. (n=60)

Variable	Categories	No response or Clinical response	Clinical remission	Total	P-Value
Age	≤30	12 (34.3)	12 (48.0)	24 (40.0)	0.285
	>30	23 (65.7)	13 (52.0)	36 (60.0)	
Sex	Male	17 (48.6)	12 (48.0)	29 (48.3)	0.965
	Female	18 (51.4)	13 (52.0)	31 (51.7)	
Smoking	No	27 (77.1)	19 (76.0)	46 (76.7)	0.918
	Yes	8 (22.9)	6 (24.0)	14 (23.3)	
Duration of disease (n=59)	2–5 years	15 (42.9)	9 (37.5)	24 (40.7)	0.681
	>5 years	20 (57.1)	15 (62.5)	35 (59.3)	
Disease extent	Proctitis or left sided	12 (34.3)	11 (44.0)	23 (38.3)	0.445
	Extensive	23 (65.7)	14 (56.0)	37 (61.7)	
Extraintestinal manifestations	No	28 (80.0)	21 (84.0)	49 (81.7)	0.748*
	Yes	7 (20.0)	4 (16.0)	11 (18.3)	

Variable	Categories	No response or Clinical response	Clinical remission	Total	P-Value
Prior biologics use	No	9 (25.7)	16 (64.0)	25 (41.7)	0.003
	Yes	26 (74.3)	9 (36.0)	35 (58.3)	
Steroids use with Tofacitinib	No	23 (65.7)	22 (88.0)	45 (75.0)	0.049
	Yes	12 (34.3)	3 (12.0)	15 (25.0)	
5-ASA use with Tofacitinib	No	22 (62.9)	17 (68.0)	39 (65.0)	0.681
	Yes	13 (37.1)	8 (32.0)	21 (35.0)	
Reduction in CRP (n= 46)	No improvement	10 (38.5)	0 (0.0)	10 (21.7)	0.002*
	Improvement or normal	16 (61.5)	20 (100)	36 (78.3)	

**Using Fisher's exact test.*

Table 6 Proportion of Patients Achieving Clinical Remission by 26 Weeks. (n=60)

Variable	Categories	No response or Clinical response	Clinical remission	Total	P-Value
Age	≤30	10 (38.5)	14 (41.2)	24 (40.0)	0.832
	>30	16 (61.5)	20 (58.8)	36 (60.0)	
Sex	Male	13 (50.0)	16 (47.1)	29 (48.3)	0.821
	Female	13 (50.0)	18 (52.9)	31 (51.7)	
Smoking	No	22 (84.6)	24 (70.6)	46 (76.7)	0.203
	Yes	4 (15.4)	10 (29.4)	14 (23.3)	
Duration of disease (n=59)	2–5 years	14 (56)	10 (29.4)	24 (40.7)	0.040
	>5 years	11 (44)	24 (70.6)	35 (59.3)	
Disease extent	Proctitis or left sided	7 (26.9)	16 (47.1)	23 (38.3)	0.112
	Extensive	19 (73.1)	18 (52.9)	37 (61.7)	
Extraintestinal manifestations	No	20 (76.9)	29 (85.3)	49 (81.7)	0.507*
	Yes	6 (23.1)	5 (14.7)	11 (18.3)	
Prior biologics use	No	5 (19.2)	20 (58.8)	25 (41.7)	0.002
	Yes	21 (80.8)	14 (41.2)	35 (58.3)	
Steroids use with	No	19 (73.1)	26 (76.5)	45 (75.0)	0.764
	Yes	7 (26.9)	8 (23.5)	15 (25.0)	
5-ASA use with	No	16 (61.5)	23 (67.6)	39 (65.0)	0.623
	Yes	10 (38.5)	11 (32.4)	21 (35.0)	
Reduction in CRP (n= 46)	No improvement	9 (47.4)	1 (3.7)	10 (21.7)	0.001*
	Improvement or normal	10 (52.6)	26 (96.3)	36 (78.3)	

**Using Fisher's exact test*

Table 7 Proportion of Patients Achieving Clinical Remission by 52 weeks. (n=55)

Variable	Categories	No response or Clinical response	Clinical remission	Total	P-Value
Age	≤30	12 (50)	11 (35.5)	23 (41.8)	0.279
	>30	12 (50)	20 (64.5)	32 (58.2)	
Sex	Male	13 (54.2)	15 (48.4)	28 (50.9)	0.671
	Female	11 (45.8)	16 (51.6)	27 (49.1)	
Smoking	No	19 (79.2)	23 (74.2)	42 (76.4)	0.667
	Yes	5 (20.8)	8 (25.8)	13 (23.6)	
Duration of disease (n=54)	2–5 years	12 (52.2)	9 (29)	21 (38.9)	0.085
	>5 years	11 (47.8)	22 (71)	33 (61.1)	
Disease extent	Proctitis or left sided	6 (25)	14 (45.2)	20 (36.4)	0.123
	Extensive	18 (75)	17 (54.8)	35 (63.6)	
Extraintestinal manifestations	No	19 (79.2)	25 (80.6)	44 (80)	1.000*
	Yes	5 (20.8)	6 (19.4)	11 (20)	
Prior biologics use	No	7 (29.2)	17 (54.8)	24 (43.6)	0.057
	Yes	17 (70.8)	14 (45.2)	31 (56.4)	
Steroids use with	No	16 (66.7)	24 (77.4)	40 (72.7)	0.375
	Yes	8 (33.3)	7 (22.6)	15 (27.3)	
5-ASA use with	No	18 (75)	18 (58.1)	36 (65.5)	0.190
	Yes	6 (25)	13 (41.9)	19 (34.5)	
Reduction in CRP (n= 43)	No	9 (50)	1 (4)	10 (23.3)	0.001*
	Improvement or normal	9 (50)	24 (96)	33 (76.7)	

** Using Fisher's exact test.*

Table 8 Odds Ratio for Achieving Clinical Remission Based on Patients' Demographics and Disease Specification

Variables	Categories	Adj. OR (95% CI)		P-value
Age	≤30	1		
	>30	5.252	(0.485, 56.828)	0.172
Sex	Male	1		
	Female	7.581	(0.785, 73.188)	0.08
Duration of disease (n=47)	2–5 years	1		
	>5 years	5.373	(0.755, 38.242)	0.093
Disease extent	Proctitis or left sided	1		
	Extensive	1.520	(0.209, 11.072)	0.679
Prior biologics use	No	1		
	Yes	.092	(0.010, 0.864)	0.037
Reduction in CRP	No improvement	1		
	Improvement or normal	78.473	(2.094, 2940.317)	0.018

10.3.2. Patients achieving endoscopic remission and response

Endoscopic remission (endoscopic Mayo score of 0 or 1) was observed in 46.7% of patients (Table 9). The reduction of CRP was a significant variable to reach endoscopic remission in the Odds ratio calculation (Table 10). The main difference in baseline characteristics to achieve clinical or endoscopic remission was found in the prior use of biologics and reduction in CRP (Table 11).

Table 9 Proportion of Patients Achieving Endoscopic Remission and Response in Ulcerative Colitis as Determined by the Endoscopic Mayo Score at 24 Weeks. (n=48)

Variable	Categories	Score of 0 or 1	Score of 2 or 3	Total	P-Value
Age	≤30	13 (46.4)	7 (35.0)	20 (41.7)	0.428
	>30	15 (53.6)	13 (65.0)	28 (58.3)	
Sex	Male	13 (46.4)	11 (55.0)	24 (50.0)	0.558
	Female	15 (53.6)	9 (45.0)	24 (50.0)	
Smoking	No	21 (75.0)	17 (85.0)	38 (79.2)	0.488[a]
	Yes	7 (25.0)	3 (15.0)	10 (20.8)	
Duration of disease (n=47)	2–5 years	10 (35.7)	8 (42.1)	18 (38.3)	0.658
	>5 years	18 (64.3)	11 (57.9)	29 (61.7)	
Disease extent	Proctitis or left sided	11 (39.3)	6 (30.0)	17 (35.4)	0.507
	Extensive	17 (60.7)	14 (70.0)	31 (64.6)	

Variable	Categories	Score of 0 or 1	Score of 2 or 3	Total	P-Value
Extraintestinal manifestations	No	25 (89.3)	15 (75.0)	40 (83.3)	0.25*
	Yes	3 (10.7)	5 (25.0)	8 (16.7)	
Prior biologics use	No	17 (60.7)	5 (25.0)	22 (45.8)	0.014
	Yes	11 (39.3)	15 (75.0)	26 (54.2)	
Steroids use with Tofacitinib	No	20 (71.4)	15 (75.0)	35 (72.9)	0.784
	Yes	8 (28.6)	5 (25.0)	13 (27.1)	
5-ASA use with Tofacitinib	No	20 (71.4)	11 (55.0)	31 (64.6)	0.241
	Yes	8 (28.6)	9 (45.0)	17 (35.4)	
Reduction in CRP (n=38)	No	2 (8.3)	7 (50.0)	9 (23.7)	0.006*
	Improvement or normal	22 (91.7)	7 (50.0)	29 (76.3)	

**Using Fisher's exact test.*

Table 10 Odds Ratio for Achieving Endoscopic Remission Based on Patients' Demographics and Disease Specification

Variables	Categories	Adj. OR (95% CI)		P-value
Age	≤30	1		
	>30	0.403	(0.039, 4.186)	0.447
Sex	Male	1		
	Female	3.006	(0.443, 20.405)	0.260
Duration of disease (n=47)	2–5 years	1		
	>5 years	3.733	(0.462, 30.150)	0.216
Disease extent	Proctitis or left sided	1		
	Extensive	1.475	(0.204, 10.691)	0.700
Prior biologics use	No	1		
	Yes	0.146	(0.019, 1.112)	0.063
Reduction in CRP	No improvement	1		
	Improvement or normal	19.027	(1.637, 221.087)	0.019

Table 11 Difference in Disease Baseline Characteristics and Treatment Specifications Between Patients Achieving Clinical and Endoscopic Remissions and Those Not Achieving Them. (n=53)

Variable	Categories	No clinical and/or endoscopic remission	Clinical and endoscopic remission	Total	P-Value
Age	≤30	13 (44.8)	10 (41.7)	23 (43.4)	0.817
	>30	16 (55.2)	14 (58.3)	30 (56.6)	
Sex	Male	16 (55.2)	11 (45.8)	27 (50.9)	0.498
	Female	13 (44.8)	13 (54.2)	26 (49.1)	
Smoking	No	22 (75.9)	18 (75.0)	40 (75.5)	0.942
	Yes	7 (24.1)	6 (25.0)	13 (24.5)	
Duration of disease (n=52)	2–5 years	13 (46.4)	8 (33.3)	21 (40.4)	0.337
	>5 years	15 (53.6)	16 (66.7)	31 (59.6)	
Disease extent	Proctitis or left sided	9 (31.0)	9 (37.5)	18 (34.0)	0.621
	Extensive	20 (69.0)	15 (62.5)	35 (66.0)	
Extraintestinal manifestations	No	23 (79.3)	21 (87.5)	44 (83.0)	0.487*
	Yes	6 (20.7)	3 (12.5)	9 (17.0)	
Prior biologics use	No	9 (31.0)	15 (62.5)	24 (45.3)	0.022
	Yes	20 (69.0)	9 (37.5)	29 (54.7)	
Steroids use with	No	21 (72.4)	17 (70.8)	38 (71.7)	0.899
	Yes	8 (27.6)	7 (29.2)	15 (28.3)	
5-ASA use with	No	19 (65.5)	16 (66.7)	35 (66.0)	0.930
	Yes	10 (34.5)	8 (33.3)	18 (34.0)	
Reduction in CRP (n=42)	No	9 (42.9)	1 (4.8)	10 (23.8)	0.004
	Improvement or normal	12 (57.1)	20 (95.2)	32 (76.2)	

**Using Fisher's exact test.*

10.3.3. Patients Still on Tofacitinib Treatment Sfter 12 Months

Of all the patients (n=60) in the AUB database who were on tofacitinib between 2018-2021, 21 patients discontinued treatment (Figure 1). The mean duration of therapy for patients remaining on treatment was around 2 years (24.3 ± 9.5 months), and less than a year (10.4 ± 6.1 months) for those who stopped treatment. The reduction of CRP was a significant factor (p=0.008) to determine if patients would be more likely to remain on tofacitinib or to discontinue treatment (Table 12).

Figure 1. Persistence on Tofacitinib in the Study Cohort at One Year Stratified by Biologics-Exposure

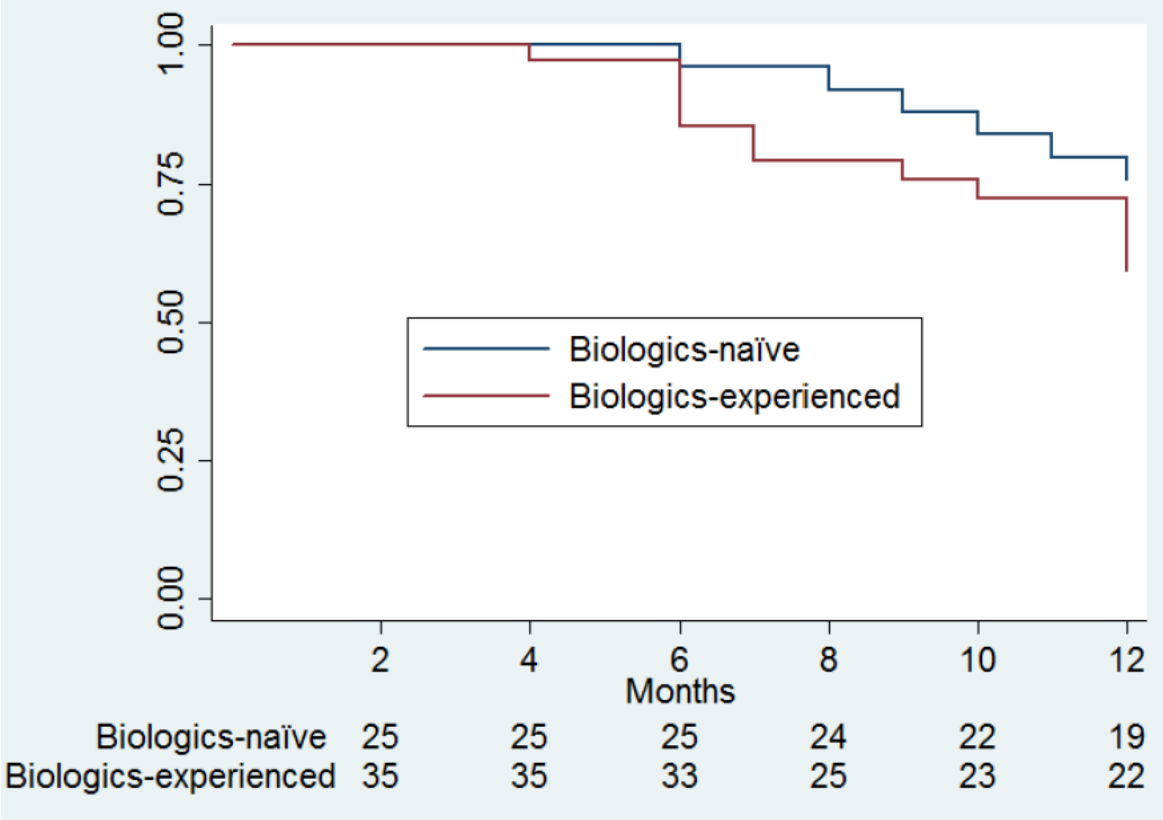

Table 12 Proportion of Patients That are Still on Tofacitinib Treatment at 1 Year. (n=60)

Variable	Categories	Remained on	Discontinued Tofacitinib	Total	P-Value
Age	≤30	14 (35.9)	10 (47.6)	24 (40)	0.377
	>30	25 (64.1)	11 (52.4)	36 (60)	
Sex	Male	16 (41)	13 (61.9)	29 (48.3)	0.123
	Female	23 (59)	8 (38.1)	31 (51.7)	
Smoking	No	31 (79.5)	15 (71.4)	46 (76.7)	0.532*
	Yes	8 (20.5)	6 (28.6)	14 (23.3)	
Duration of disease (n=59)	2–5 years	14 (35.9)	10 (50)	24 (40.7)	0.297
	>5 years	25 (64.1)	10 (50)	35 (59.3)	
Disease extent	Proctitis or left sided	18 (46.2)	5 (23.8)	23 (38.3)	0.090
	Extensive	21 (53.8)	16 (76.2)	37 (61.7)	
Extraintestinal manifestations	No	32 (82.1)	17 (81)	49 (81.7)	1.000*
	Yes	7 (17.9)	4 (19)	11 (18.3)	

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Variable	Categories	Remained on	Discontinued Tofacitinib	Total	P-Value
Prior biologics use	No	19 (48.7)	6 (28.6)	25 (41.7)	0.131
	Yes	20 (51.3)	15 (71.4)	35 (58.3)	
Steroids use with Tofacitinib	No	32 (82.1)	13 (61.9)	45 (75)	0.086
	Yes	7 (17.9)	8 (38.1)	15 (25)	
5-ASA use with Tofacitinib	No	23 (59)	16 (76.2)	39 (65)	0.182
	Yes	16 (41)	5 (23.8)	21 (35)	
Reduction in CRP (n=46)	No	3 (9.7)	7 (46.7)	10 (21.7)	0.008*
	Improvement or normal	28 (90.3)	8 (53.3)	36 (78.3)	

**Using Fisher's exact test.*

10.3.4. Patients Requiring Inflammatory Bowel Disease Surgery After 12 Months

Table 13 Proportion of Patients Requiring IBD Surgery After 1 Year of Follow up. (n=21)

Referred for surgery if stopped treatment?	No	17 (81.0)
	Yes	4 (19.0)

10.3.5. Changes in Laboratory Results

Table 14 Changes in Calprotectin at 12 Weeks Compared to Baseline Following Treatment with Tofacitinib

Calprotectin at baseline	Not done	35 (58.3)
	Normal	1 (1.7)
	High	24 (40)
Calprotectin at 12 weeks	Not done	40 (66.7)
	Normal	11 (18.3)
	High	9 (15)
Calprotectin change	Data unavailable	44 (73.3)
	Stayed normal	0 (0)
	Stayed abnormal	9 (15.0)
	Improvement*	7 (11.7)
	Worsening&	0 (0)

* Changing from abnormal to normal.
& Changing from normal to abnormal.

Table 15 Changes in C-Reactive Protein (CRP) at 12 Weeks Compared to Baseline Following Treatment with Tofacitinib (n=60)

CRP at baseline	Not done	8 (13.3)
	Normal	11 (18.3)
	High	41 (68.3)
CRP at 12 weeks	Not done	11 (18.3)
	Normal	30 (50)
	High	19 (31.7)
CRP change	Data unavailable	14 (23.3)
	Stayed normal	6 (10.0)
	Stayed abnormal	16 (26.7)
	Improvement*	23 (38.3)
	Worsening&	1 (1.7)

* Changing from abnormal to normal.
& Changing from normal to abnormal.

Table 16 Changes in Hemoglobin at 12 Weeks Compared to Baseline Following Treatment with Tofacitinib (n=60)

Hemoglobin at baseline	Not done	8 (13.3)
	Normal	29 (48.3)
	High	23 (38.3)
Hemoglobin at 12 weeks	Not done	13 (21.7)
	Normal	34 (56.7)
	High	13 (21.7)
Hemoglobin change	Data unavailable	15 (25.0)
	Stayed normal	23 (38.3)
	Stayed abnormal	13 (21.7)
	Improvement*	9 (15.0)
	Worsening&	0 (0)

* Changing from abnormal to normal.
& Changing from normal to abnormal.

Table 17 Changes in Low-Density Lipoprotein (LDL) at 12 Weeks Compared to Baseline Following Treatment with Tofacitinib (n=60)

LDL at baseline	Not done	46 (76.7)
	Normal	12 (20)
	High	2 (3.3)
LDL at 12 weeks	Not done	45 (75)
	Normal	12 (20)
	High	3 (5)
LDL change	Data unavailable	52 (86.7)
	Stayed normal	7 (11.7)
	Stayed abnormal	1 (1.7)
	Improvement*	0 (0)
	Worsening&	0 (0)

* Changing from abnormal to normal.
& Changing from normal to abnormal.

10.4. Adverse Events/Adverse Reactions

There were 2 AEs (1 lymphopenia and 1 facial acne) identified during unstructured data review based on explicit attribution to tofacitinib therapy.

Table 18 Number and Category of Adverse Drug Reactions

Number of patients with Adverse drug reactions	No	58 (96.7)
	Yes	2 (3.3)
Adverse event type (n=2)		
	Not infectious (facial acne and lymphopenia)	2

11. DISCUSSION

Since the release of tofacitinib in the market, many real-world studies have attempted to evaluate its effectiveness and safety. However, our study is the first to discuss this in a MENA (Middle East and North Africa) region. This is a multicenter real-world evidence (RWE) study of UC patients with moderately severe disease prescribed tofacitinib in Lebanon during the past 3 years and followed up for at least 6 weeks.

The sample size of our study is comparable to most other real-world evidence studies on tofacitinib in UC patients who have moderate to severe disease. Most patients had either pancolitis or left sided disease with endoscopic mayo score of 2 or 3 at the time of initiation. Also, more than half of them had failed one or more biologic therapy. This is also similar to most other previously reported RWE studies.

In a study conducted by Straatmijer et al. between 2018 and 2019,[3] 39% of patients had clinical and endoscopic remission at one-year follow-up, which is similar to our result of 40%. Also, the cessation of tofacitinib was seen in only one-third of the patients in both studies. In Straatmijer's study,[3] it was reported that patients who failed prior anti-TNF were less likely to discontinue treatment. However, the sample size in this study was 36 patients with 89% of them with prior anti-TNF failure. This leaves only 4 patients without prior anti-TNF failure, which does not allow to draw any meaningful conclusions.

Another study that was done at multiple centers in the UK (4) found that 74% of the patients responded initially to tofacitinib, compared to 92% in our study. However, the percentage of patients who had steroid-free remission at week 26 was 44%, which is the same result as our study at the same time point.

In a study conducted by Lair-Mehiri et al.,[5] the reported steroid-free clinical remission at 1 year was similar to our study (34% vs 43%). In this study, surgery free survival was also observed, and it was found that 70% of patients avoided colectomy at 1 year, compared to 81% in our study.

A meta-analysis of RWE studies of tofacitinib in UC patients was done by Lucaciu et al.,[6] and included 830 patients from 9 different studies. Clinical response and remission rates at 8 weeks were very similar to the rates found in our study sample (51% and 37% vs 50% and 42%). Rates for response and remission at the median follow-up of 24 weeks was somewhat different than our rates at 26 weeks (40% and 29% vs 28% and 57%), however, the discontinuation of treatment was observed in around one third of the patients in both studies.

With regards to the clinical and endoscopic evaluations from our study compared with the first trial on tofacitinib conducted on 194 UC patients in 2012, comparable results were noted. Clinical remission at 8 weeks was achieved in 48% and 41% of patients on low and high doses of tofacitinib respectively, compared to 41.7% in our sample at the same time point. As for endoscopic evaluation, 61% of the low dose, and 78% of the high dose of the sample in the trial reached endoscopic remission after 8 weeks. In contrast, around 58% of our sample reached endoscopic remission at 26 weeks. This difference might be due to different observation times after treatment initiation, as patients can initially respond then fail the treatment.

In our study, we explored potential explanatory variables for clinical and endoscopic remissions. One important factor was the prior use of biologics; patients who are biologics experienced were less likely to achieve remission than biologics-naïve patients. On multivariate analysis, two variables were consistently associated with clinical and endoscopic remissions: biologic-naive status and a documented reduction in CRP. Patients who received prior biologics were 10 times less likely to achieve clinical remission at 1 year (OR = 0.092, 95% CI = 0.010, 0.864) than biologic-naïve patients. Patients with normalization or reduction in CRP values had higher odds (OR = 78.47, 95% CI =2.094, 2940.317) than patients with no improvement in CRP at achieving clinical remission at 1 year. Similarly, patients with normalization or reduction in CRP were 19 times more likely to achieve endoscopic remission (OR =19.027, 95% CI = 1.637, 221.087). When looking at both clinical and

endoscopic remission, biologic-experienced patients were less likely to achieve this composite endpoint (OR = 0.09, 95% CI = 0.012, 0.655) than biologic-naïve patients. Patients with normalization or reduction in CRP had higher odds (OR = 40.548, 95% CI =1.945, 845.151) than patients with no improvement in CRP in achieving this composite endpoint of clinical and endoscopic remission. However, more studies are needed to evaluate and validate this finding as this effect has not been observed/analyzed in prior real-world evidence studies.

11.1. Key Results

Tofacitinib appears to be effective in the treatment of UC patients in this real world cohort. Predictors of clinical and endoscopic remissions were biologic-naïve status and reduction in CRP. Observed Adverse drug reactions were consistent with the known safety profile.

11.2. Strength and Limitations

One of the major limitations of this study is the low number of patients enrolled. In fact, the number of patients was less than expected at study design and onset. Reasons behind this can be attributed to the economic crisis in Lebanon, termination of financial coverage of the drug by the ministry of health and insurance companies, and the departure of many gastroenterologists and patients from the country, limiting assessment at different endpoint. Nonetheless, compared to other real-world evidence studies on tofacitinib, our study had higher or similar numbers.

Also, as a retrospective study, some data were missing for a few variables. Patients in our sample were followed by different gastroenterologists who adopted different practice methodologies. As such, some potentially interesting laboratory values and follow-ups in the patient population (ie, LDL, calprotectin, endoscopy follow-up etc) were not available at all varying time points of the study.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

In conclusion, this study showed similar results to other real-world evidence studies conducted on tofacitinib in UC patients in terms of clinical and endoscopic responses and remissions as well as the safety profile. Larger studies and longer follow-up of real-world evidence should provide further insight regarding effectiveness and safety.

14. REFERENCES

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15. LIST OF SOURCE TABLES AND FIGURES

Not applicable, all tables are in the study report body.

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