NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

PASS Information

Title	An evaluation of early use patterns to assess the effectiveness of Xeljanz® (tofacitinib citrate) in rheumatoid arthritis: A retrospective non-interventional database study of observational data embedded within Optimising Patient outcome in Australian RheumatoLogy - Quality Use of Medicines Initiative (OPAL-QUMI)
Protocol number	A3921292
Version identifier of the final study report	1.0
Date	07 June 2021
EU Post Authorization Study (PAS) register number	EUPAS18435
Active substance	Tofacitinib citrate
Medicinal product	Xeljanz®
Product reference	Not Applicable
Procedure number	Not applicable
Marketing Authorization Holder (MAH)	Pfizer Limited
Joint PASS	No
Research question and objectives	To understand the treatment patterns (line of therapy, combination with other therapies or monotherapy), clinical effectiveness, patient reported outcomes and treatment adherence of Australian adult patients with rheumatoid arthritis who are receiving tofacitinib.

Redacted

	To describe the safety profile of tofacitinib in Australian adult patients with rheumatoid arthritis.
Country(-ies) of study	Australia
Author	Redacted [redacted]

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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
ATC	Anatomical Therapeutic Chemical
bDMARD	Biologic Disease-Modifying Anti-Rheumatic Drug
CDAI	Clinical Disease Activity Index
cDMARD	Conventional Disease-Modifying Anti-Rheumatic Drug
CRP	C-Reactive Protein
DAS28	Disease Activity Score for Rheumatoid Arthritis
DMARD	Disease-Modifying Anti-Rheumatic Drug
ESR	Erythrocyte Sedimentation Rate
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
GPP	Good Pharmacoepidemiology Practices
HAQ-DI	Health Assessment Questionnaire – Disease Index
HCRU	Health Care Resource Utilisation
HL7	Health Level Seven
HREC	Human Research Ethics Committee
ICD-10	International Classification of Diseases 10
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for PharmacoEpidemiology
JAK	Janus Kinase
LOINC	Logical Observation Identifiers Names and Codes
MP	Multiprocessor
NIS	Non-Interventional Study
NSAID	Non-Steroidal Anti-Inflammatory Drug
OPAL	Optimising Patient outcome in Australian rheumatoLogy
PASS	Post-Authorisation Safety Study
PBS	Pharmaceutical Benefits Scheme
PRO	Patient Reported Outcome
QOL	Quality of Life
QUMI	Quality Use of Medicines Initiative
RA	Rheumatoid Arthritis
S4S	Software 4 Specialists (Clinical Software Developers For OPAL)
SAP	Statistical Analysis Plan
SDAI	Simple Disease Activity Index
SJC	Swollen Joint Count

Abbreviation	Definition
TJC	Tender Joint Count
tsDMARD	Targeted Synthetic Disease Modifying Anti-Rheumatic Drug
VAS	Visual Analogue Scale
WHO	World Health Organisation

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Redacted		

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>	30 March 2017		
Start of data collection	31 March 2017		
End of data collection	01 September 2018		
<Registration in the EU PAS register>	31 March 2017		
<Study progress report I>			
Interim report I: 1st data cut	01 March 2017		
Interim report II: 2nd data cut	01 September 2017	30 November 2017	
Interim report III: 3rd data cut	01 March 2018	24 August 2018	
Final report of study results	01 March 2019	07 June 2021	

6. RATIONALE AND BACKGROUND

Rheumatoid diseases such as rheumatoid arthritis (RA) have a significant negative impact on patients' health-related quality of life (QOL), and present a significant economic burden. Maximisation of health-related QOL is the primary goal of treatment. This is achieved through symptom and inflammation control, prevention of progressive structural damage, preservation or normalisation of function and social participation, and targeting remission.[1,2] Treatment of RA usually involves a multifaceted approach that includes pharmacologic and non-pharmacologic strategies. Non-pharmacologic therapy may include physical, occupational, and psychological therapy, and surgery, while pharmacological therapy usually consists of various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids, and synthetic or biologic disease modifying anti-rheumatic drugs (DMARDs).

Recently, a new oral targeted synthetic DMARD (tsDMARD), tofacitinib, has become available. Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome. It was approved for use in Australia in February 2015 and included in the Pharmaceutical Benefits Scheme (PBS) (reimbursement) in October 2015. Limited data exist to describe the characteristics and outcomes of patients who receive tofacitinib in the real-world setting.

Patient Reported Outcomes (PROs) complement physician and laboratory measures in providing scientific evidence to support decisions regarding clinical therapy. The Outcome Measures in Rheumatology International consensus effort, the American College of Rheumatology, and the European League Against Rheumatism have recognized the importance of including a variety of PROs in randomized controlled trials.[3,4,5]

This study aims to use the Optimising Patient outcome in Australian rheumatoLogy (OPAL) registry to provide real-world evidence regarding general treatment patterns, clinical effectiveness, treatment adherence and PROs among RA patients being treated with tofacitinib in the post-approval setting. Similar data will be collected for patients treated with bDMARDs to provide context in a real-world clinical practice setting. No formal comparisons between patients treated with tofacitinib and bDMARDs will be performed.

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

7. RESEARCH QUESTION AND OBJECTIVES

Research Question

To understand the patterns of treatment (lines of therapy, and use as combination or monotherapy), clinical effectiveness, PROs and treatment adherence among Australian adult patients with RA treated with tofacitinib. Similar data will also be collected for patients treated with bDMARDs to provide descriptive information about clinical management of RA in real-world Australian clinical practice.

Objectives

The primary objectives of the study are:

1. To describe tofacitinib treatment patterns among Australian adult patients with RA, which are defined as follows:
    - Line of usage (eg, first-line, second-line) and dosing patterns;
    - Use as monotherapy and in combination with cDMARDs;
    - Reasons for discontinuation of tofacitinib.
2. To assess the clinical effectiveness of tofacitinib, as defined by disease severity markers (DAS28, CDAI, SDAI) and percent of patients reaching targeted treatment goals (remission or low disease activity), in Australia.
3. To assess PROs (HAQ-DI, FACIT-Fatigue, HCRU) and treatment adherence in Australian adult patients with RA who are prescribed tofacitinib.

Secondary objectives are:

1. To describe bDMARD treatment patterns among Australian adult patients with RA, which are defined as follows:
    - Line of usage (eg, first-line, second-line) and dosing patterns;
    - Use as monotherapy or in combination with cDMARDs;
    - Reasons for discontinuation of bDMARD.
2. To assess PROs (HAQ-DI, FACIT-Fatigue, HCRU) and treatment adherence in Australian adult patients with RA who are prescribed bDMARDs.
3. To describe the safety profile of Australian adult patients with RA who have been prescribed tofacitinib.

8. AMENDMENTS AND UPDATES

None.

Redacted

9. RESEARCH METHODS

9.1. Study Design

This is a retrospective, non-interventional cohort study of treatment patterns in patients prescribed tofacitinib or bDMARDs, and will involve extracting real-world patient data from the Australian OPAL registry. Data will be extracted for the period 01 February 2015 until 01 September 2018.

All drugs will be prescribed and all follow-up visits will be captured as part of normal medical practice. Patient therapeutic strategies will not be determined by the study protocol.

9.2. Setting

Data will be extracted from the Australian OPAL registry database. The OPAL database collects information from individual clinicians' servers during routine clinical consultations, using purpose-built worksheets in Audit4 software. Pathology and imaging reports are electronically transferred from the pathology and radiology providers and are incorporated into the patient's medical record. This software serves as the patient's medical record.[2]

The activities of OPAL Rheumatology Ltd have received overarching ethics approval from the University of New South Wales Human Research Ethics Committee, based on a patient opt-out arrangement. De-identified data are exported from the clinician's server and encrypted. Aggregated data are sent to the OPAL Study Committee and study statistician. All research undertaken by OPAL requires the prospective approval of a properly constituted Australian Human Research Ethics Committee.

The database has collected information on more than 32,000 patients from 42 rheumatologist clinics (and approximately 80 individual rheumatologists) around Australia. Of these 23,000 have a diagnosis of RA.

Tofacitinib was approved by the Therapeutic Goods Administration in February 2015, so the start of the sample selection window will correspond to the time of approval.

The sample selection window is 01 February 2015 to 01 September 2017. Patients will be followed for a minimum one year, so the sampling window is 01 February 2015 to 01 September 2018.

It is estimated that approximately 500 patients taking tofacitinib, and more than 2,500 patients taking bDMARDs will be enrolled in this study, however all relevant available data will be extracted. Data cuts occur in March 2017, September 2017, March 2018 and September 2018.

This study includes adult patients (aged 18 years or older) with a diagnosis of RA, who have received treatment with tofacitinib or a bDMARD and have at least 1 year of follow-up.

9.3. Subjects

9.3.1. Inclusion Criteria

Patients must meet all the following inclusion criteria to be eligible for inclusion in the study:

1. Diagnosed with RA, based on DAS28;
2. At least 18 years of age on the date of commencement of tofacitinib or a bDMARD;
3. Received at least one prescription for tofacitinib or a bDMARD; and
4. Have at least 1 year of follow-up since prescription of the index DMARD (tofacitinib or a bDMARD).

9.3.2. Exclusion Criteria

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

1. Diagnosis with any autoimmune rheumatic disease or inflammatory bowel disease except for RA (eg, psoriatic arthritis, ankylosing spondylitis, psoriasis Crohn's disease or ulcerative colitis).

9.3.3. Propensity Score Matching

Because of the observational nature of the data, analyses will be repeated both in the overall population, and also in a propensity score matched population. Propensity score matching increases the comparability of the observed baseline characteristics in patients treated with tofacitinib and bDMARDs. The propensity score is the conditional probability of receiving treatment (eg, tofacitinib versus other biologic agent), which is estimated using logistic regression.

The following independent covariates will be included as predictor variables in the propensity score:

- Patient age group at index.
  - 18-34.
  - 35-44.
  - 45-54.
  - 55-64.
  - 65-74.
  - >75.

- Sex.
  - Male
  - Female
- DAS28.
- Select baseline treatments combinations (where baseline is the index date).
  - Methotrexate monotherapy.
  - Methotrexate + other conventional DMARD(s).
  - Conventional DMARD(S) other than methotrexate.
  - Neither methotrexate nor other conventional DMARD(s).

Tofacitinib users will be matched to bDMARD through propensity score matching in a ratio of one tofacitinib user to five bDMARD users (1:5). The use of an initial caliper width of 0.20 is recommended. Matching will be determined by examining the propensity score distribution (density plot) in both the original sample and the matched sample, and by comparing standardized difference (in means and proportions) between the groups on the matched cohort; a difference above 0.1 is considered indicative of substantial difference in that covariate.[7] In addition, characteristics will be compared using chi-square, t statistics, and standardized differences.

In the comparative secondary outcomes, regression adjustment will be used to reduce bias due to residual differences (imbalance) in observed baseline covariates between the two treatment groups ie, those variables where a substantial difference still exists after matching will be included in any formal analyses as covariates.

Propensity score matching might not be feasible for reasons such as insufficient sample size within treatment groups of interest or insufficient overlap between groups (a loss of 50% or more tofacitinib patients ie, there are zero appropriate matches found for over 50% of tofacitinib patients during the propensity score matching exercise). In this case, only descriptive analyses will be conducted rather than matching analyses.

Further information on the propensity score matching method is available in the Statistical Analysis Plan (SAP).

9.4. Variables

The primary exposure of interest is an initial prescription for tofacitinib or a bDMARD identified during the sample selection window. The date of the first prescription after the start of the sample selection window will serve as the study index date and the beginning of the post-index period.

Index DMARD: the agent of interest identified during the sample selection window (01 February 2015 to 01 September 2017) using Anatomical Therapeutic Chemical (ATC) codes. If the patient has been prescribed more than one of the drugs of interest (ie, tofacitinib or bDMARD), the index DMARD will be considered tofacitinib for those ever receiving tofacitinib, or the first prescription of a bDMARD ('bDMARD group') if the patient has never received tofacitinib.

9.4.1. Exposure

Prior to the full assessment of the outcomes related to the exposure, the prescription data will be evaluated for missing data (eg, strength, or quantity) and to identify implausible values (eg, usually high quantity, or dosage). Implausible values will be adjudicated by two experienced rheumatologists who are members of the OPAL board and independent of the Sponsor. The recommended dosing schedule for tofacitinib and bDMARD is shown in Table 1.

Table 1. Recommended Dosage for DMARDs

Agent	Recommended Dose*
Abatacept	Weight based dosing (500 mg if <60 kg; 750 mg if 60 to 100 kg; 1 g if >100 kg) administered as intravenous infusion over 30 minutes.
Adalimumab	40 mg sc fortnightly, or 40 mg weekly in patients not taking methotrexate.
Anakinra	100 mg per day administered as a subcutaneous injection.
Certolizumab	400 mg (as 2 injections of 200 mg each on one day) at Weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every 2 weeks. Alternatively, a maintenance dose of 400 mg every 4 weeks may be given.
Etanercept	50 mg weekly given as a subcutaneous injection, either once weekly as a single injection or twice weekly as two separate 25 mg injections given 3 to 4 days apart.
Golimumab	50 mg given as a subcutaneous injection once a month, on the same date each month.
Infliximab	Patients not previously treated with infliximab: initially 3 mg/kg to be followed with additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion then 8 weeks thereafter. Doses may be adjusted in increments of 1.5 mg/kg up to a maximum of 7.5 mg/kg.

Agent	Recommended Dose*
Rituximab	1,000 mg by intravenous infusion followed by 1,000 mg by intravenous infusion two weeks later.
Tocilizumab	8 mg/kg every four weeks as an intravenous infusion, with doses not exceeding 800 mg, or 162 mg weekly subcutaneously.
Tofacitinib	5 mg twice daily orally.

*Recommended dose based on Australian prescribing information.

9.4.2. Baseline

Baseline characteristics of interest are listed in Table 2. Baseline is defined as the measurements taken at the index date, or the closest measurement before the index date.

Table 2. Baseline Characteristics

Variable	Role	Data source(s)	Operational definition
Baseline Health	Baseline characteristic	OPAL	Presence of comorbidities
Clinical characteristics	Baseline characteristic	OPAL	Disease duration, disease severity, disease activity (DAS28, SDAI, CDAI, Tender Joint Count (TJC), Swollen Joint Count (SJC))
Health assessment	Baseline characteristic	OPAL	General health (HAQ-DI, Visual Analogue Scale (VAS))
Patient reported outcomes and treatments	Baseline characteristic	OPAL	Number, sequence and duration of previous DMARDs (HAQ-DI, HCRU, FACIT-fatigue)
Treatment history	Baseline characteristic, potential confounder	OPAL	Dose and prior duration of treatment with DMARDs
Concomitant therapy	Baseline characteristic, potential confounder	OPAL	Type and dose of concomitant cDMARDs

9.4.3. Outcomes

Analyses will be presented for the overall population and for the propensity score match population.

9.4.3.1. Treatment Patterns

Treatment patterns for patients in the 'tofacitinib group' and the 'bDMARD group' will include line of usage, dose, frequency, and concomitant cDMARDs. Reasons for discontinuation will be collected.

9.4.3.2. Clinical Effectiveness

Clinical effectiveness will be assessed using disease severity (remission, low, moderate, high), DAS28, CDAI and SDAI scores. The proportion of patients reaching targeted treatment goals will be reported.

9.4.3.3. Patient Reported Outcomes

Patient reported outcomes include Health Assessment Questionnaire for rheumatoid arthritis (HAQ-DI) score, Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT Fatigue) score, and Health-care resource use questionnaire (HCRU) score.

9.4.3.4. Safety

Safety variables include adverse events.

9.5. Data Sources and Measurement

De-identified data will be extracted from the OPAL database. Permission to extract the data from the individual clinician's Audit4 software is obtained three to four weeks prior to the data extraction.

The sample selection window will be 01 February 2015 to 01 September 2017 and all patient with a bDMARD prescription during this time who meet the other eligibility criteria will be included in the extracted data set. A minimum of one year will occur for all sampled patients and therefore data up to 01 September 2018 will be included in the study.

The number and percentage of missing values will be included in the description of baseline characteristics. Missing values will not be imputed.

The patterns and predictors of missing variables will be explored for those covariates with 10% or greater missing values.

Analyses will be conducted using Stata Multiprocessor (MP) V14 (or higher), or equivalent statistical software.

9.6. Study Size

Data will be extracted for at least 500 tofacitinib and 2,500 bDMARD patients. A sample size of 500 and 2,500 patients, respectively, would ensure acceptably precise estimates of treatment patterns and clinical effectiveness.

The study will continue until one year follow up has been achieved for at least 500 tofacitinib and 2,500 bDMARD patients. Patients who discontinue tofacitinib will also be followed up for at least 1 year.

9.7. Data Transformation

De-identified data will be extracted from the OPAL database. Permission to extract the data from the individual clinician's Audit4 software is obtained three to four weeks prior to the data extraction.

The sample selection window will be 01 February 2015 to 01 September 2017 and all patient with a bDMARD prescription during this time who meet the other eligibility criteria will be included in the extracted data set. A minimum of one year will occur for all sampled patients and therefore data up to 01 September 2018 will be included in the study.

The number and percentage of missing values will be included in the description of baseline characteristics. Missing values will not be imputed.

The patterns and predictors of missing variables will be explored for those covariates with 10% or greater missing values.

Analyses will be conducted using Stata Multiprocessor (MP) V14 (or higher), or equivalent statistical software.

Detailed methodology for data transformations, particularly complex transformations (eg, many raw variables used to derive an analytic variable), are documented in the statistical analysis plan (SAP), which is dated, filed and maintained by the sponsor.

9.8. Statistical Methods

Patients meeting the inclusion and exclusion criteria described above will be categorised into one of two mutually exclusive drug cohorts, based on the type of DMARD received:

- Tofacitinib.
- All bDMARDs.

Baseline has been defined in Section 9.4.2.

All continuous variables will be summarised using n (non-missing sample size), mean, standard deviation, median, minimum and maximum. The frequency and percentages (based on the non-missing sample size) or observed levels will be reported for all categorical measures.

Descriptive summaries will be produced for each data cut, providing there is sufficient data available, and again at the final analysis.

All summaries are descriptive and there are no comparative analyses being undertaken, therefore, no adjustments for multiple data cuts and multiple endpoints are required.

Patients who discontinue their index treatment (tofacitinib or bDMARD) will continue to be followed for a period of 1 year.

Further information, and sample tables can be found in the SAP.

9.8.1. Main Summary Measures

9.8.1.1. Patient Demographics

Patient demographics will be summarised descriptively. Data will be presented overall, and by treatment group (tofacitinib and bDMARD).

9.8.1.2. Treatment Patterns

The number of patients prescribed tofacitinib or another bDMARD will be summarised. Information on length of follow-up (eg, mean, standard deviation, median, minimum, maximum) for the tofacitinib and bDMARD groups will be calculated. Adherence to treatment will be calculated.

Further information can be found in the SAP.

9.8.1.3. Clinical Effectiveness

The following summaries will be performed for patients in the tofacitinib treatment group. Summaries will be performed at baseline, 12, 24, 52, 78, 104 weeks with change from baseline also summarised at each post-baseline time point.

- DAS28.
- DAS28 change from baseline.
- CDAI.
- CDAI change from baseline.
- SDAI.
- SDAI change from baseline.
- Number and % of patients reaching targeted treatment goals.

9.8.1.4. Patient Reported Outcomes

The following summaries will be performed for patients in the tofacitinib treatment group. Summaries will be performed at baseline, 12, 24, 52, 78, 104 weeks with change from baseline also summarised at each post-baseline time point.

- HAQ-DI.

- HAQ-DI change from baseline.
- FACIT-Fatigue.
- FACIT-Fatigue change from baseline.
- HCRU.
- HCRU change from baseline.

9.8.1.5. Safety

Exploratory and descriptive analysis of the most common adverse events (eg, infections) will be performed. No specific categories are prospectively planned, but more detailed evaluations will be undertaken if any safety signals are identified. These detailed evaluations will not involve review of unstructured data from patient records. Briefly, the clinical software developers for OPAL, Software 4 Specialists (S4S) will identify the centers and treating physicians corresponding to the patients with the safety signal. OPAL will send an investigative guideline to the treating physician who will perform the requested investigations and record the data on OPAL. Afterwards, S4S will extract and de-identify all the data from these patients and OPAL will review the de-identified and aggregated data.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8.2. Main Statistical Methods

The primary exposure of interest was an initial prescription for tofacitinib or a bDMARD identified during the sample selection window. The date of the first prescription after the start of the sample selection window served as the study index date and the beginning of the post-index period. Patients that had received a prescription of tofacitinib during the sample selection window were considered part of the "tofacitinib group" even if they had also been prescribed a DMARD. All other patients were considered to be in the bDMARD group. Patients who discontinued treatment were followed up for a minimum period of 1 year from their date on index. Data was evaluated for missing data and to identify implausible values. Implausible values were adjudicated by two rheumatologists, who were members of OPAL but independent of the sponsor. Treatment effectiveness was evaluated from baseline (index date) to 18 months using Disease Activity Score-28 with erythrocyte sedimentation rate (DAS28-ESR) and Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) measures. An exploratory and descriptive analysis of the most common adverse events was performed. Treatment persistence with the index DMARD, in part a surrogate for efficacy, was defined as the time (in consecutive days from treatment initiation until treatment discontinuation. Duration of treatment of the index DMARD was summarized

using Kaplan-Meier estimates of treatment persistence. Treatment pattern evaluation included percentage of patients receiving monotherapy or conventional synthetic DMARD (csDMARD) combination therapy at treatment initiation and at 19- to 26-month follow-up. No formal comparisons were made between patients treated with tofacitinib and bDMARDs. Any numerical differences or trends were descriptive.

9.8.3. Missing Values

None.

9.8.4. Sensitivity Analyses

None.

9.8.5. Amendments to the Statistical Analysis Plan

None.

9.9. Quality Control

The Audit4 software is used at the point of care, and as such is a source document. Thus the data that is provided by clinicians to OPAL is a subset of the data that is a legal document which the clinician must ensure is accurate. For chemical pathology results, Audit4 has an internal quality control and only accepts values in the database where there is a corresponding Logical Observation Identifiers Names and Codes (LOINC) code and matching units as provided in the Health Level Seven (HL7) message from the pathology provider service. No additional formal quality control procedures are in place for OPAL.

9.10. Protection of Human Subjects

Subject information and consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The activities of OPAL Rheumatology Ltd have received overarching ethics approval from the University of New South Wales Human Research Ethics Committee, based on a patient opt-out arrangement. De-identified data are exported from the clinician's server; encrypted and aggregated data are sent to the OPAL Study Committee and study statistician. All research undertaken by OPAL requires the prospective approval of a properly constituted Australian Human Research Ethics Committee. This study does not require additional informed consent to be obtained from patients.

Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians. At no time during the study will the sponsor receive patient identifying information.

Ethics approval will be sought by OPAL Rheumatology Ltd.

10. RESULTS

10.1. Participants

A planned sample size of 500 and 2500 patients, in the tofacitinib and bDMARD groups respectively, would ensure acceptably precise estimates of treatment patterns and clinical effectiveness. Data was extracted for 652 patients administered tofacitinib and 2158 patients administered bDMARDs. Though the bDMARD sample size was smaller than planned, this sample size still ensured clinically acceptable precision in the estimates of treatment patterns and clinical effectiveness; for example, for a proportion of 30%, the confidence interval is 28 to 32% for samples of 2500 or 2158.

10.2. Descriptive Data

Table 1 Patient demographics and disease characteristics at baseline for the propensity score matched population

	bDMARD				Tofacitinib			
N (%)	1300 (66.7)				650 (33.3)			
Age at index (years)								
Mean (SD)	60.8 (13.1)				61.0 (12.7)			
Median (min, max)	62 (21, 92)				63 (23, 89)			
Gender, *n* (% of column)								
Female	1056 (81.2%)				528 (81.2%)			
Disease duration in months, median	107 [*N* = 818]				120 [*N* = 411]			
Disease status								
DAS28-CRP, *n* (% of column)	*N* = 542				*N* = 304			
	Rem	Low	Mod	High	Rem	Low	Mod	High
	88 (16.2)	48 (8.9)	185 (34.1)	221 (40.8)	54 (17.8)	26 (8.6)	109 (35.9)	115 (37.8)
CDAI, *n* (% of column)	*N* = 533				*N* = 308			
	Rem	Low	Mod	High	Rem	Low	Mod	High
	37 (6.9)	82 (15.4)	131 (24.6)	283 (53.1)	20 (6.5)	53 (17.2)	78 (25.3)	157 (51.0)
TJC28, mean (SD)	9.17 (8.65) [N = 783]				8.42 (8.24) [N = 402]			
SJC28, mean (SD)	9.03 (8.47) [*N* = 783]				8.18 (8.09) [*N* = 402]			
RAPID3, mean (SD)	3.58 (2.58) [*N* = 126]				4.39 (2.25) [N = 54]			
Baseline treatment combinations[a]								
Methotrexate + cDMARD	294 (22.6%)				146 (22.5%)			
Methotrexate alone	300 (23.1%)				150 (23.1%)			
cDMARD (excluding methotrexate)	142 (10.9%)				72 (11.1%)			
bDMARD monotherapy	564 (43.4%)				282 (43.4%)			
Missing	–				–			

[a] Monotherapy was assigned for patients who were treated with a bDMARD or tsDMARD but had no record of methotrexate or alternative cDMARD at the time of index. It is not clear, therefore, whether this is the true proportion of patients with monotherapy, or whether it represents missing information. Missing represents patients with no information in the Medication dataset. These patients received bDMARD or tsDMARD but have no concomitant medication reported

Redacted

10.3. Outcome Data

10.4. Main Results

From March 2015 to September 2018, 2810 patients initiated tofacitinib or bDMARDs and met the initial study selection criteria. Overall, 2158 (77%) patients received index treatment with bDMARDs and 652 (23%) patients received index treatment with tofacitinib. The matched population included 1950 patients (1300 bDMARD initiators and 650 tofacitinib initiators). Participant demographics for the matched population are reported in Table 1. Patients were predominantly aged 55 to 74 years (57.8%), and female (81.2%). Baseline comorbidities (not shown) were well matched across bDMARD and tofacitinib groups. The disease status was similar between the two groups and the treatment combinations were also well matched at index between the two groups. At index, in the matched population, median disease duration was 107 months and 120 months (p = 0.037), for the bDMARD and tofacitinib groups, respectively. In the overall population, median disease duration was 100 months and 120 months (p = 0.002) for the bDMARD and tofacitinib groups, respectively (data not shown).

Treatment effectiveness

In the matched population, the percentage of patients achieving DAS28-ESR disease remission and low disease activity (LDA) are shown in Figure 1. Only patients with baseline DAS28-ESR data are represented. At index, 16.1% (n = 87/539) and 17.3% (n = 52/300) of patients were in DAS28-ESR remission for the bDMARD and tofacitinib groups, respectively. After 3 months of treatment, 49.1% (n = 157/320) and 49.7% (n = 73/147) had achieved DAS28-ESR remission and after 18 months of treatment, 52.4% (n = 89/170) and 57.8% (n = 48/83) of patients had achieved DAS28-ESR remission in the bDMARD and tofacitinib groups, respectively. There were no significant differences in remission rates between the bDMARD and tofacitinib groups at any of these time points (p = 0.66, p = 0.90, and p = 0.41 at index, 3 months, and 18 months respectively). At index, 7.4% (n = 40/539) and 8.0% (n = 24/300) of patients were in DAS28-ESR LDA for the bDMARD and tofacitinib groups, respectively. After 18 months of treatment 14.1% (n = 24/170) and 10.8% (n = 9/83) of patients were in DAS28-ESR LDA in the bDMARD and tofacitinib groups, respectively. There were no significant differences in LDA rate between the bDMARD and tofacitinib groups at any of these time points (p = 0.76 and p = 0.47, at index and 18 months respectively). The percentage of patients in the matched population achieving CDAI and SDAI disease remission activity is shown in Figure 2. At 18 months, the percentage of patients achieving CDAI and SDAI remission was similar with 29.0% (n = 51/176) and 29.2% (n = 50/171) bDMARD patients and 30.5% (n = 25/82) and 30.9% (n = 25/81) tofacitinib patients reporting CDAI or SDAI remission, respectively (p = 0.80 and p = 0.79, respectively).

No adverse events were reported in more than 5% of the population for bDMARD or tofacitinib treatment for the overall or the matched population.

Figure 1. Percentage of Patients in the Propensity Score Matched Population Achieving DAS28-ESR (a) Disease Remission and (b) Low Disease Activity (LDA)

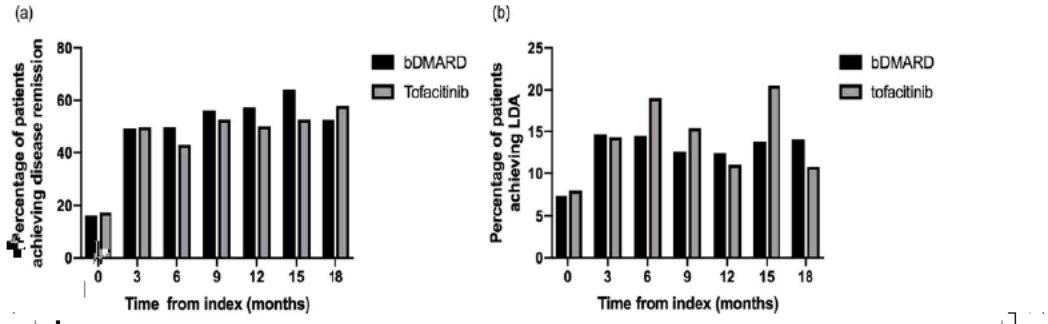

Fig. 1 Percentage of patients in the propensity score matched population achieving DAS28-ESR **a** disease remission and **b** low disease activity (LDA)

Figure 2. Percentage of Patients in the Propensity Score Match Population Achieving (a) CDAS and (b) SDAI Disease Remission

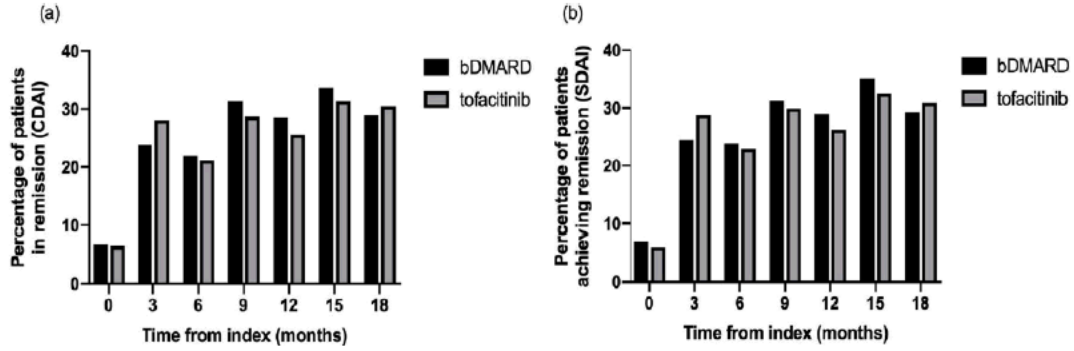

Fig. 2 Percentage of patients in the propensity score matched population achieving **a** CDAI and **b** SDAI disease remission

Treatment persistence

The median persistence of treatment for the matched population was 33.8 months (95% CI 28.8 to 40.4) for patients prescribed bDMARDs and was 34.2 months (95% CI 32.2 to "not reached") for patients prescribed tofacitinib (Figure 3). The difference in median persistence between groups was not significant (p = 0.19, log rank test). In the propensity score matched population, the most common reasons for discontinuation were completion of treatment (429/1300 (33%), 135/650 (25%)), lack of efficacy (281/1300 (22%), 113/650 (17%)), lack of efficacy, secondary failure (213/1300 (16%), 63/650 (10%)), and adverse reaction (211/1300 (16%), 81/650 (12%)), in the bDMARD and tofacitinib arms, respectively. Note patients could have more than one reason for discontinuation recorded.

Figure 3. Treatment Persistence in the Propensity Score Matched Population for bDMARD and Tofacitinib

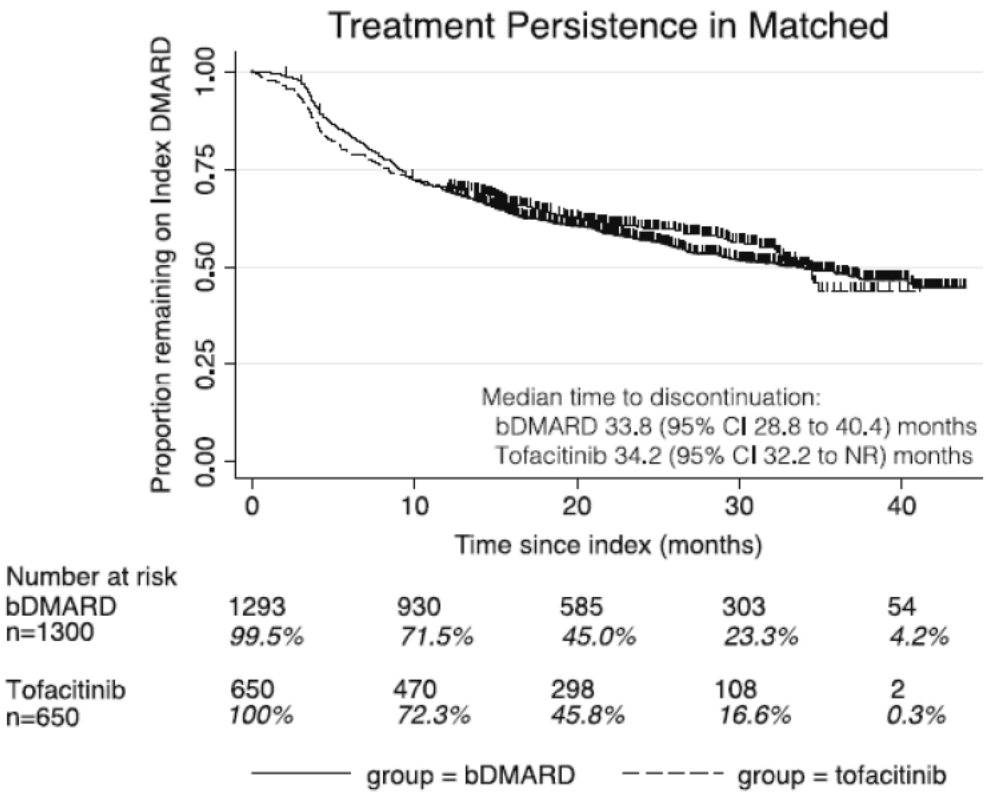

Fig. 3 Treatment persistence in the propensity score matched population for bDMARD and tofacitinib

Treatment patterns

Monotherapy and combination cDMARD therapy treatment patterns are shown in Table 2 for the overall population. At index, more patients were prescribed tofacitinib as monotherapy (43.4%, n = 282/650) compared with bDMARD monotherapy (33.4%, n = 719/2154; p <0.001). For patients remaining on index tofacitinib or index bDMARD at 19 to 26 months of follow-up, the percentage of patients on monotherapy increased for both groups (tofacitinib 49.1% (n = 208/424); bDMARD 39.0% (n = 518/1329) (p <0.001)). Corticosteroid use was similar at index for both groups (tofacitinib 35.6% (n = 232/652); bDMARD 34.2% (n = 738/. 2158)) and similar at 18 months of treatment (tofacitinib 34.3% (n = 185/540); bDMARD 32.1% (n = 567/1764); p =0.51 and 0.36). (Data not shown).

Please refer to publication attached for data references above.

10.5. Other Analyses

None.

10.6. Adverse Events/Adverse Reactions

No safety data were collected in this study.

11. DISCUSSION

11.1. Key Results

This study of real-world treatment in Australian patients with RA found that tofacitinib demonstrated treatment effectiveness and persistence that was similar to bDMARDs. Similar persistence between tofacitinib and bDMARDs has also been observed in other real-world studies.[6,7] The criteria for reimbursement in Australia require that patients demonstrate a response to treatment within 3 months. The small reduction in persistence observed at 3 months in both treatment arms may be due to those patients who had not responded adequately to treatment by 3 months and were no longer eligible for receiving government-subsided treatment. Patients that initiated tofacitinib at index had longer disease duration than patients that initiated bDMARD treatment. This has also been observed for patients in the US Corrona dataset where the mean disease duration was significantly longer for initiators of tofacitinib (13.9 years) compared with initiators of bDMARDs (9.9 years, $p < 0.001$).[8] The longer duration of disease for patients that initiated tofacitinib may reflect that tofacitinib has only recently become available compared with other bDMARD therapy. Patientsmay have been waiting for a therapy with a new mode of action because they were not responsive to other bDMARDs. It may also reflect that some patients may have been waiting to use orally administered tofacitinib rather than use an injectable bDMARD. There was a trend for a greater use of tofacitinib as monotherapy compared with bDMARDs. Observational studies in the USA have also observed that tofacitinib was used more commonly as monotherapy than bDMARDs.[6,8,9] The results from this study suggest that tofacitinib is an effective and enduring intervention in RAwith tofacitinib persistence and effectiveness comparable to bDMARDs. Future research could focus on trying to identify factors associated with lack of persistence. “missing not at random” data occur. We assume, given the source of this data however, that data are likely to be missing at random, as important clinical information is likely to have been recorded within the patient’s notes. In addition, the Pharmaceutical Benefits Scheme only requires a total joint count/swollen joint count along with ESR or CRP, and as such the patient global VAS is often not clinically recorded, so a DAS-28 score cannot be calculated. Propensity score matching was not possible using the DAS28-ESR score due to insufficient numbers.

11.2. Limitations

This is a retrospective study based on data in the OPAL registry. The analyses are therefore limited by the availability of data in this database. Data fields in the Audit4 software are not mandatory so there will likely be missing data points. The sample size, variables, and study duration have been selected to minimize the impact of this.

The Audit4 software records medically significant events, which are not necessarily serious adverse events and therefore it will be not be possible to stratify data into serious and non-serious adverse events.

The source data will be subject to logic checks in the software programming and individual clinicians are responsible for accurate data entry. Patient classifications are based solely on the physician's diagnosis.

The database only covers outpatient visits; inpatient visits are not included in this analysis.

12. OTHER INFORMATION

Not Applicable.

13. CONCLUSIONS

Tofacitinib demonstrated treatment effectiveness and persistence similar to bDMARDs. Overall, there was a trend for more use of tofacitinib as monotherapy than bDMARDs.

14. REFERENCES

15. LIST OF SOURCE TABLES AND FIGURES

Please refer to publication manuscript.[10]

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Signed By:	Date(GMT)	Signing Capacity
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