NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title:

Real-world evaluation of effectiveness, persistence, and usage patterns of tofacitinib in treatment of psoriatic arthritis in Australia.

Date:

19 July 2022

Name and Affiliation of the Main Author:

RedactedRedactedRedactedRedactedRedactedRedactedRedactedRedacted
Redacted

Keywords:

tofacitinib citrate; medication effectiveness; treatment response; healthcare utilization; healthcare impact

Rationale and Background:

Chronic inflammatory diseases such as psoriatic arthritis (PsA) 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] Treatment of PsA 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, tofacitinib, a new oral, targeted synthetic DMARD (tsDMARD), has become available for the treatment of PsA. 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 May 2018 and included in the Pharmaceutical Benefits Scheme (PBS) (reimbursement) in May 2019. 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.[2]

This study aimed to use the Optimising Patient outcome in Australian rheumatoLogy (OPAL)3 dataset to provide real-world evidence regarding general treatment patterns, clinical effectiveness, treatment persistence and PROs among PsA patients being treated with tofacitinib in the post-approval setting. Similar data were collected for patients treated with bDMARDs that provides context from a real-world clinical practice setting. No formal comparisons between patients treated with tofacitinib and bDMARDs were performed. An exploratory analysis and description of the most common reasons for discontinuation of treatments are described. No safety analysis or analysis of adverse events were performed.

Research Question and Objectives:

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

Study Design:

This was a retrospective non-interventional secondary structured data analysis cohort study of treatment patterns in 1,486 Australian adult patients prescribed IL17i, TNFi, or tofacitinib and involved extracting real-world patient data from the Australian OPAL dataset. Tofacitinib was listed on the Pharmaceutical Benefits Scheme (PBS) in May 2019. TNFi (adalimumab, certolizumab, etanercept, golimumab infliximab) and IL17i (secukinumab, ixekizumab) were already listed on the Pharmaceutical Benefits Scheme at this time. Data were extracted for the period 01 May 2019 until 30 September 2021 (sample window). Included patients were followed for a minimum of 1 year following their prescription of the index DMARD (IL17i, TNFi, or tofacitinib). Patients who discontinued their index DMARD were also followed up for at least 1 year from the time of the initial prescription of that treatment.

Setting:

Data were extracted from the Australian OPAL dataset database.

Subjects and Study Size, Including Dropouts:

The study involves data from 1,486 adult patients ≥18 years of age, but under 95 years, diagnosed with psoriatic arthritis (PsA), who received treatment with IL17Ai, TNFi, or tofacitinib sample selection window 01 May 2019 until 30 September 2021 were included in the study and followed for at least 1 year. Only incident users of tofacitinib (ie, those who were first prescribed tofacitinib within the sample selection window and after being enrolled into OPAL) with data before the tofacitinib prescription being available within OPAL were

selected. Similarly, patients newly prescribed an IL-17Ai or TNFi during the sample selection window were also included.

Patients who had no visit data recorded and patients who had missing start dates for any biologic treatment were excluded. Enrolled in the study were 406 patients prescribed tofacitinib, and 1,080 patients prescribed other bDMARDs (IL17Ai, TNFi). Follow up and enrollment were continued beyond the timelines detailed in the "Milestones" section of the protocol, if required, to achieve at least one year follow up for the 406 tofacitinib and 1,080 other bDMARD patients. Analysis was based on a data cut undertaken in September 2020 and September 2021.

Patients registered in the OPAL dataset and meeting all the following inclusion criteria were selected for study inclusion: 1. Diagnosed with PsA. 2. Aged 18 years but under 95 years of age on the index date (date of commencement of IL17Ai, TNFi, or tofacitinib). 3. Received at least one prescription for IL17Ai, TNFi, or tofacitinib; and 4. Have at least 1 year of follow-up since prescription of IL17Ai, TNFi, or tofacitinib. 5. Patients meeting any of the following criteria will not be included in the study: 6. Diagnosis with any autoimmune rheumatic disease except for PsA (eg, rheumatoid arthritis, ankylosing spondylitis). 7. Patients who have no visit data recorded within the sample window. 8. Patients who have missing start dates for IL17Ai, TNFi, or tofacitinib during the sample selection window.

The sample selection window was 01 May 2019 to 30 September 2021. Patients were followed for a minimum of one year. Therefore, the sampling window was 01 May 2019 to 30 September 2022. The data source: the data were extracted from the Australian OPAL dataset. The OPAL dataset 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. [1]

Variables:

The following variables were analysed: exposure (tofacitinib or bDMARDs), baseline characteristics (eg, baseline health, treatment history, clinical characteristics, PROs, treatment history) and outcomes (treatment patterns, clinical effectiveness, and PROs).

Data Sources:

All data for this study will be obtained from the OPAL dataset. The OPAL – Quality Use of Medicines Initiative is a point of care observational database.[1] *Currently approximately 104 Australian rheumatologists and more than 192,000 patients with rheumatic disease are participating in the dataset. Data are captured into individual clinician's servers during routine clinical consultations, using the purpose-built worksheets in the Audit4 software.*[4] *Data de-identified for patient, clinic and clinician are exported from each of the OPAL member's local server to a central server for analysis.*

Study Size:

With 406 tofacitinib patients, proportions (eg, the proportion of first line users) were estimated with a precision (ie, standard error of the estimate) of at worst ±7%. This is based on an estimated proportion of 50%.

Data Analysis:

Descriptive summaries were performed for each data cut and at the final analysis. No comparative analyses were undertaken. Analyses were repeated in the overall population and the propensity score matched the population.

The baseline demographic characteristics of each patient were extracted based on data captured on the index date, or the closest measurements prior to the index date. These data include age, sex, and baseline comorbidities. The clinical characteristics of each patient include the time since symptom onset at index, disease severity: the DAS28-ESR/DAS28-CRP, the Clinical Disease Activity Index (CDAI), the Simple disease activity index (SDAI), the DAPSA, the Health assessment questionnaire for disease index (HAQ-DI), the Health-care resource use questionnaire (HCRU), the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue), and the Baseline medication of interest: NSAIDs/analgesics; Corticosteroids; Disease modifying antirheumatic drugs (DMARDs).

The number, sequence, and duration of previous DMARDs were collected. The duration of the current bDMARD prior to the index date, and the number and dose of concurrent conventional DMARDs were also collected. The prior biologic treatment information on the number of prior bDMARD treatments was summarised. For the episodes of prior biologic treatment, the number falling into each of the following categories was summarised: Combination – with methotrexate (MTX) and a cDMARD; combination – with MTX only; combination – with cDMARD only; Monotherapy.

Treatment Information:

The number of patients prescribed the index DMARD in each treatment group were summarised together with information on length of follow-up. The following summaries were performed to assess the treatment patterns for patients in the IL17i, TNFi or tofacitinib treatment groups. The dose of the index DMARD, line of use and concomitant cDMARD use were summarised at the index date. The number and percentage of subjects in each treatment group falling into the following categories at the index date are summarized: Combination – with MTX and a cDMARD; Combination – with MTX only; Combination – with cDMARD only; Monotherapy.

The demographic characteristics of patients in each of the above categories were examined. Duration of treatment of the index DMARD was summarised using Kaplan-Meier (KM) methods where subjects who had not discontinued were censored at the last available assessment. In addition, for those receiving monotherapy treatment at the index date,

duration of monotherapy treatment (ie, until either a switch to combination therapy with the same index DMARD or until discontinuation of the index DMARD) were summarised. Similarly, for those receiving combination treatment at the index date, duration of combination treatment with the index DMARD were summarised. Reasons for discontinuation were also summarised overall and by treatment combination (monotherapy, combination therapy).

The Baseline is defined as the measurements taken at the index date, or the closest measurement before the index date. The Outcomes Analyses were presented for the overall population and for the propensity score match population. The Treatment Patterns for patients in the 'tofacitinib group' the 'TNFi group' and 'IL17i group' includes the line of usage, dose, frequency, and concomitant cDMARDs. Reasons for discontinuation were collected. The Clinical Effectiveness was assessed using the disease severity (remission, low, moderate, high), the DAS28, the CDAI, the SDAI and the DAPSA scores. The proportion of patients reaching targeted treatment goals was reported. Patient Reported Outcomes: include the health assessment questionnaire for disease index (HAQ-DI) score, the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) score, and the Health Care Resource Utilisation (HCRU) score.

Data Sources:

All data for this study were obtained from the OPAL dataset. The OPAL – Quality Use of Medicines Initiative is a point of care observational dataset database.[3,4] Approximately, 104 Australian rheumatologists and more than 192,000 unique patients with rheumatic disease participates in the dataset. Participating rheumatologists use an electronic patient management program that captures patient and disease-specific details during routine physician-patient consultations. OPAL members are based largely in private practice; however, this is representative of the Australian rheumatology community. OPAL members run clinics and collect data from both urban and rural clinics. Data are captured into individual clinician's servers during routine clinical consultations, using the purpose-built worksheets in the Audit4 software.[3] Audit4 serves as the patient's medical record and produces the clinical correspondence for the consultation.

Diagnoses are made by individual rheumatologists rather than being criteria based. Pathology and imaging reports are electronically transferred from the providers and incorporated into the patient's medical record. The primary rheumatological condition and comorbidities are coded using the World Health Organisation (WHO) International Classification of Diseases 10 (ICD-10), and medications are mapped to the WHO Anatomical Therapeutic Chemical (classification) (ATC) System. There are condition specific "clinical worksheets" such as a homunculus for tender and swollen joint counts, visual analogue scales, and automatic calculation of DAS28 (Erythrocyte Sedimentation Rate (ESR) or C-reactive protein (CRP)). Data de-identified for patient, clinic and clinician

can be exported from each of the OPAL member's local server to a central server for analysis based on a predefined ethics-approved protocol.

Study Size Sample: Size calculations are not applicable. However, with 406 tofacitinib patients, proportions (eg, the proportion of first line users) were estimated with a precision (ie, standard error of the estimate) of at worst ±7%. This was based on an estimated proportion of 50%. For lower or higher estimates, the precision was improved.

The size of the propensity score matched the population of tofacitinib and IL17i /TNFi users may have been smaller than this ie, if not all tofacitinib patients could be found matches)

Data Management: De-identified data were extracted from the OPAL database. Permission to extract the data from the individual clinician's Audit4 software was obtained 3 to 4 weeks prior to the data extraction. The sample selection window was 01 May 2019 to 30 Sept 2020, and all patients with a bDMARD prescription during this time who meet the other eligibility criteria were included in the extracted data set. A minimum of 1 year occurred for all sampled patients. Therefore, data up to 30 September 2021 were included in the study. The number and percentage of missing values were included in the description of baseline characteristics. Missing values were not imputed. The patterns and predictors of missing variables were explored for those covariates with 10% or greater missing values.

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

Data Analysis: Patients meeting the inclusion and exclusion criteria were categorised into 1 of 2 mutually exclusive drug cohorts, based on the type of DMARD received: Tofacitinib; All bDMARDs. All continuous variables were 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 were reported for all categorical measures. Descriptive summaries were produced for each data cut, providing there was sufficient data available, and again at the final analysis. All summaries are descriptive, and there were no comparative analyses undertaken. Therefore, no adjustments for multiple data cuts and multiple endpoints were required.

Patients who discontinued their index treatment (tofacitinib, TNFi or IL17i) were followed for a 1-year period. Detailed methodology for summary and statistical analyses of data collected in this study are documented in a statistical analysis plan (SAP), which is dated, filed, and maintained by the sponsor. The SAP modified the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses are reflected in a protocol amendment.

Patient Demographics: The patient demographics were summarised descriptively. Data were presented, overall, and by treatment group (tofacitinib and bDMARD).

Treatment Patterns: The number of patients prescribed tofacitinib or another bDMARD were summarised. Information on length of follow-up (eg, mean, standard deviation, median, minimum, maximum) for the tofacitinib and bDMARD groups were calculated. Persistence to treatment was calculated. Further information can be found in the SAP.

Clinical Effectiveness: The following summaries were performed for patients in the tofacitinib treatment group. Summaries were performed at baseline, 3, 9, 15, and 24 months with change from baseline also summarised at each post-baseline time-point. The DAS28; DAS28 change from baseline; CDAI; CDAI change from baseline; SDAI; SDAI change from baseline; DAPSA; DAPSA change from baseline; Number and % of patients reaching targeted treatment goals.

Patient Reported Outcomes:

The following summaries were performed for patients in the tofacitinib treatment group. Summaries were performed at baseline, 3, 9, 15, and 24 months 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.

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 were in place for OPAL.

Limitations of the Research Methods:

This is a retrospective study based on data in the OPAL dataset. The analyses were therefore limited by the availability of data in this database. Data fields in the Audit4 software are not mandatory. So, it is likely to be missing data points. The sample size, variables, and study duration were selected to minimize the impact of this. The Audit4 software records medically significant events, which are not necessarily serious adverse events (AE). Therefore, it was not possible to stratify data into serious and non-serious AE.

The source data were subject to logic checks in the software programming, and individual clinicians were responsible for accurate data entry. Patient classifications were based solely on the physician's diagnosis. The database only covered outpatient visits: inpatient visits were not included in this analysis.

PROTECTION OF HUMAN SUBJECTS

Patient Information:

This study involved data that exist in anonymized structured format and contains no patient personal information.

Patient Consent:

As this study involves anonymized structured data, which according to applicable legal requirements, do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer was not required.

Patient Withdrawal:

Not applicable for this study.

Institutional Review Board: (IRB)/Independent Ethics Committee (IEC) The activities of OPAL Rheumatology Ltd have received overarching ethics approval from University of New South Wales Human Research Ethics. There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

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 follows generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE).[6]

MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involved data that exist as structured data from the time of study start, or a combination of existing structured data, and unstructured data, which were converted to structured form during the implementation of the protocol, solely, by a computer using automated/algorithmic methods, such as natural language processing.

From these data sources, individual patient data were not retrieved, or validated. Therefore, it was not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) could not be met.

PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This protocol was registered on the Register of Post-Authorisation Studies. A clinical study report of all results was generated, and results of this study will be submitted to a peer-reviewed journal. Authorship of the manuscript is based on International Committee of Medical Journal Editors (ICMJE) criteria.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer will be informed immediately.

Milestones:

Final study report completed by November 2022.

Other Aspects:

Not applicable.

Results

1. OUTCOMES:

The primary objective of the study was to understand the treatment patterns (lines of therapy, in combination with other therapies or monotherapy), clinical effectiveness, patient reported outcomes and treatment persistence among Australian adult patients with psoriatic arthritis who are receiving tofacitinib by describing tofacitinib, interleukin 17 inhibitor (IL17i), and tumor necrosis factor inhibitor (TNFi) treatment patterns among these patients with PsA, including: Line of use (eg, first-line, second-line); Mean dose; Proportion of patients receiving monotherapy; Proportion of patients using in combination with NSAIDs, corticosteroids and conventional disease-modifying antirheumatic drugs (cDMARDs); Reasons for discontinuation.

The secondary objective of the study was to: 1. To describe treatment persistence to IL17i, TNFi and tofacitinib in Australian patients with PsA. 2. To describe the clinical effectiveness of tofacitinib, IL17i, and TNFi, as defined by disease severity markers Disease Activity Score in 28 joints – erythrocyte sedimentation rate, (DAS28-ESR) Clinical Disease Activity Index (CDAI), Simple Disease Activity Index (SDAI), Disease Activity in Psoriatic Arthritis (DAPSA) [if available]) and the percentage of patients reaching targeted treatment goals (remission or low disease activity), in Australia.

3. *To describe patient reported outcomes (HAQ-DI, FACIT-Fatigue, HCRU) in Australian adult patients with PsA between those prescribed tofacitinib and those prescribed other IL17i, or TNFi.*

2. STATISTICAL METHODS:

A flow chart was produced showing the overall population, and then showing the subsets of patients included in each treatment group.

All continuous variables were summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum, and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels were reported for all categorical measures. In general, all data are listed, sorted by site,

treatment, and subject. All summary tables are structured with a column for 'tofacitinib group', for the 'IL-17Ai group', for the 'TNFi group' and a column for all patients.

The mean, standard deviation, and any other statistics other than quantiles, were reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum used the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (eg, regression coefficients) were reported to 3 significant figures. All analyses were conducted using STATA MP/2 v16 (StataCorp, College Station, Texas) or equivalent statistical software. All analyses are descriptive, and there were no comparative analyses undertaken. Therefore, no adjustments for multiple data cuts or multiple endpoints were required. All variables listed in Section 6 were summarised for the overall population, and by treatment group and then repeated for the matched population (by treatment group only). No formal comparisons between treatment group were conducted.

3. ETHICAL CONSIDERATIONS:

The study involved data in anonymized structured format and did not contain any personal information about the patients. The local IRB/IEC prospectively approved the study protocol, protocol amendments, and other relevant documents.

The study was conducted in accordance with legal and regulatory requirements, and in compliance with the research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), and Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

4. EFFICACY EVALUATION:

The efficacy of tofacitinib was evaluated by the following endpoints considered at baseline, 12-24 weeks, 25-52 weeks, 53-76 weeks, and 77-104 weeks with change from baseline also considered at each post baseline time point. If more than one measure was included in the dataset during the specified endpoint, then the last of the measures were included. • DAS28-ESR. • DAS28-CRP. • SDAI. • CDAI. • DAPSA. • Achievement of the targeted treatment goal of remission (only considered for patients who were not in this category at baseline by the above measures). • Achievement the targeted treatment goal of low disease (only considered for patients who were not in this category at baseline).

Patient Reported Outcomes:

The following endpoints were considered at baseline, 12-24 weeks, 25-52 weeks, 53-76 weeks, and 77-104 weeks with change from baseline also considered at each post-baseline time point. • HAQ-DI. • VAS. • FACIT-Fatigue. • HCRU.

Correlations between these outcomes and the efficacy/effectiveness endpoints listed in Section 6.2 were explored.

Safety Endpoints:

Adverse events reported in more than 5% of patients in any treatment group were summarized.

Other Endpoints:

Not applicable.

Covariates:

The covariates listed in Section 5.2 of the protocol were used in the regression model that calculates the propensity scores for matching purposes.

Handling of Missing Values:

Missing data were not imputed.

The process for dealing with missing values for the covariates used in the regression model used in the propensity score matching procedure is detailed in Section 5.2. of the protocol.

Marketing Authorization Holder(s):

For PASS reports submitted in the EU, list "Pfizer Limited", along with any other market authorization holder(s) which initiated, managed, or financed the study; addresses are not required. For PASS reports not submitted in the EU or non-PASS reports, this section can be deleted.

List of Tables and Figures:

Refer to the TOPsA Final Analysis for an extensive listing of tables and figures.

Names and Affiliations of Principal Investigators:

RedactedRedactedRedacted

RedactedRedactedRedactedRedacted

References:

1. Smolen JS, Schöls M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force [published correction appears in Ann Rheum Dis. 2018 Mar;77(3):472]. Ann Rheum Dis. 2018;77(1):3-17. doi:10.1136/annrheumdis-2017-211734.

2. Kirwan JR, Tugwell PS. Overview of the patient perspective at OMERACT 10--conceptualizing methods for developing patient-reported outcomes. J Rheumatol. 2011;38(8):1699-701.

3. Tymms K, Littlejohn G. OPAL: a clinician driven point of care observational data management consortium. Clin Exp Rheumatol. 2014;32(5 Suppl 85):S-150-2.

4. Roberts L, Arnold M, Bird P, Burnet S, De Jager J, Littlejohn G, et al. ARA-P39 Optimising patient outcomes in Australian rheumatology (OPAL) - a quality use of medicines initiative (QUMI) with >7000 rheumatoid arthritis (RA) patients. Internal medicine journal. 2011;41:9-38.

5. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424.

6. Public Policy Committee - International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol Drug Saf.