NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title:

Canadian Non-Interventional Study of Xeljanz in Rheumatoid Arthritis (CANTORAL)

Date:

01 May 2023

Name and Affiliation of The Main Author:

Redacted [redacted] *a*

Keywords:

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

Rationale and Background:

This non-interventional study was designated as a PASS and was conducted voluntarily by Pfizer.

Rheumatoid Arthritis (RA) is a chronic, auto-immune, inflammatory disease that affects approximately 1.0% of the adult Canadian population.[1] The syndrome is characterized by progressive inflammatory synovitis of the joints that can lead to erosion of the cartilage and subchondral bone.[1] As a result of these joint abnormalities patients experience functional impairment and pain that has a negative impact on quality of life, and productivity with increased morbidity and health care utilization.[2]

Management of patients with RA is focused on reducing pain and inhibition of disease progression. Early use of Disease Modifying Anti-Rheumatic Drugs (DMARDS) has been recommended in order to control disease progression.[3,4] The advent of biologic DMARDS for the management of RA has provided significant benefits to patients, and to traditional DMARDS.[5]

However, the increased risk for serious infections and malignancy and uncertainty regarding the long term sustained therapeutic response for biologic DMARDS remains a concern.[6,7]

Redacted [redacted]

In addition, the intravenous method of administration of biological DMARDS is a potential obstacle for use by patients, who tend to prefer treatment regimens that allow for at-home administration.[8] Furthermore, there is a need for an alternative treatment for patients that do not respond or lose the response with biologic DMARDS. It follows that molecules with a different mechanism of action may address this need.

Tofacitinib is an oral Janus kinase (JAK) inhibitor approved in Canada in April 2014. At the time, tofacitinib was indicated in combination with methotrexate (MTX) for reducing the severity of symptoms in patients with moderately to severely active RA who have had an inadequate response to MTX.[9] In cases of intolerance to methotrexate (MTX), physicians may consider using tofacitinib as monotherapy.[9]

On December 9th, 2021, following the assessment of results from the regulator-mandated post authorization safety study (NCT02092467),[10] the indication for moderate to severe RA was revised; the revision indicated tofacitinib, in combination with methotrexate, in adult patients with active RA who have had an inadequate response to MTX and to one or more DMARDs.[11] In cases of intolerance to methotrexate (MTX) and other DMARDs, physicians may consider use of tofacitinib as monotherapy.[11]

The mechanism of action of tofacitinib involves blocking of the immune response by inhibition of intra-cellular JAK signaling pathways.[12] This is different from that of currently available biologic DMARDS acting on the extracellular inflammatory pathways which involve pro inflammatory cytokines such as Tumor Necrosis Factor (TNF-alpha) and Interleukin (IL-6).

The results of randomized controlled trials have demonstrated the efficacy and safety of tofacitinib comparable to the biologic DMARDs.[13-18] In the aforementioned regulator mandated post-authorization safety study, which enrolled patients ≥50 years of age with additional cardiovascular risk factors, tofacitinib failed to demonstrate non-inferiority versus TNF-alpha for the co-primary endpoints of adjudicated Major Adverse Cardiovascular Events (MACE) and malignancy.[10] Data from long term observational extensions of controlled trials have shown that the real-world use of tofacitinib has a safety profile that is comparable to that observed in registrational studies and comparable to that of the currently approved biologic DMARDs.

Randomized controlled trials conducted under ideal conditions using highly selected patients allow the assessment of safety and efficacy and support decisions regarding marketing approval of treatments by regulatory agencies. The efficacy results reported in controlled clinical trials most often are not corroborated by the effectiveness observed in the real-world setting. In addition, safety signals that can be undetected in controlled clinical trials often emerge in the real – life setting. This leads to a treatment and safety gap between the results expected on the basis of controlled clinical trials and the real – world experience with marketed interventions. The causes of this discrepancy are first the difference between patients included in controlled clinical trials and those treated in the real – life setting with respect to demographics, disease severity, profile, comorbidities and concomitant medication use. Sub – optimal adherence to treatment in the real–life setting is another major contributor to the treatment gap. In addition, access to care, physician decision making, and

treatment patterns are additional important factors contributing to this phenomenon. Post Approval Clinical Epidemiological Studies (PACES), which include among others, phase IV trials, Post Marketing Non-Interventional Observational Studies and Patient Registries are the only means by which the treatment and safety gaps in real-life setting can be assessed. In addition, PACES allow the evaluation of interventions at the patient, physician, and health care system levels aimed at minimizing the treatment and safety gaps and optimizing patient management.

Regional specificity is an important element of PACES. Although PACES can be conducted on a multinational and even global scale with many objectives being contextually similar across regions, regional idiosyncrasies with respect to disease epidemiology, patient profile and behavior, physician practice patterns, and access to care prohibit the generalization of the results from one country or even region to another. Therefore, PACES were conducted at regional levels in order to address the needs of the population. Prior to the current study, there was limited data describing the characteristics and the long-term effectiveness and safety of tofacitinib treated patients in Canadian clinical practice.

The current study aimed to assess the patterns of use of tofacitinib in the management of moderate to severe RA in a real-world setting in Canada. The study also described the real-life effectiveness and safety of RA patients initiating treatment with tofacitinib in Canada. Additionally, the study evaluated determinants of optimal therapeutic response. By enrolling patients from a representative sample of academic and community rheumatologists the results are generalizable to the Canadian RA population. The non-interventional nature of the study will be protected by enrolling only patients for whom the treating physician has decided to initiate treatment with tofacitinib independently of the study. The long-term duration of patient observation extended beyond discontinuation of treatment with tofacitinib ensured that the effect of temporal changes on treatment patterns and access to care on effectiveness were assessed. The results of this comprehensive study have implications for the management of RA patients in Canada with a potential global impact.

Research Question and Objectives:

The primary objectives of this study were to describe the profile of RA patients initiating treatment with tofacitinib in the Canadian real – world/clinical setting and to describe the clinical effectiveness of tofacitinib over time in patients with moderate to severe RA in the real-world/clinical setting.

Research Method:
Study Design:

This was an observational, multi-centre study using a prospective cohort design. Patients with RA that were newly treated with tofacitinib as per the decision of their physician, in accordance with the Canadian label[9] and local practice, and who met all the identified inclusion eligible to be enrolled in the study. This was an observational study of the treating physician. Pfizer provided or paid for medicinal products for this non-interventional study.

All assessments described in this protocol were performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in the country where this non-interventional study was conducted:

As per CRA guidelines and usual clinical practice, the recommended schedule for follow-up was: Baseline, Months 3, 6 (primary endpoint), 12, for year 1, and every 6 months in subsequent years of observation. According to the non-interventional nature of the study, only information and results of assessments that were part of routine care or required for the management of the patient as per the physician's judgment, were collected during these time points. More specifically, there were no tests or clinical assessments mandated by the study. However, as part of their participation in the study, patients were asked to complete self-administered questionnaires ascertaining patient-reported outcomes (PROs) at specific time intervals.

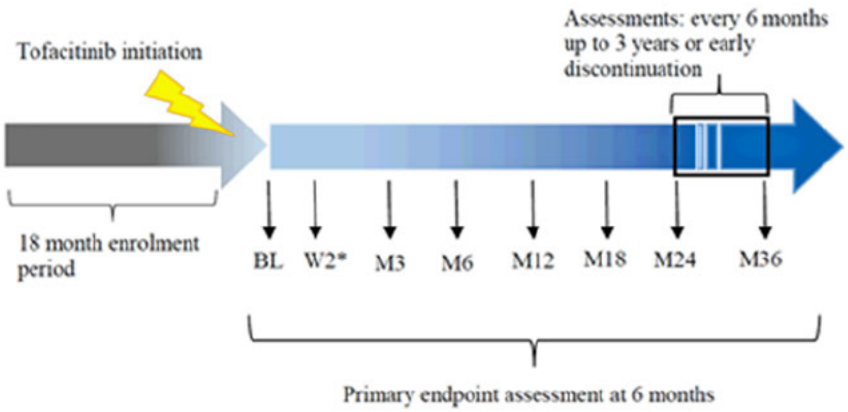
Although the actual follow-up and data collection were at the physician's discretion, the timing of study visits was expected to fall within the following defined ranges:

- *Year 1 after treatment initiation with tofacitinib: maximum 5 visits, minimum of 3 visits. Expected visits would have occurred within 30 days of 3, 6, 12 months post treatment initiation (as per CRA guidelines and usual clinical practice).*
- *Years 2 – 3: minimum of 1 visit per year.*

Unscheduled visits were permitted at the discretion of the treating physician. The reason for, and the results of any assessments performed during the unscheduled visit were documented in the CRFs.

Figure 1 *below provides a summary of the study design.*

Figure 1. Study Design



The prevalence and incidence of all types of malignancies excluding MSC were estimated within the RA cohort.

Setting:

The study was conducted in a real-world/clinical setting in Canada, with a representative sample of academic and community rheumatologists used to ensure that the findings could be applied to the country's RA population as a whole.

Subjects and Study Size, Including Dropouts:

There were 505 patients that initiated tofacitinib at baseline and that were included in the full analysis set. Baseline characteristics are shown in Table 1 below. The mean age at baseline was 59.3 years and the mean duration since rheumatoid arthritis diagnosis was 10.2 years. Most patients were also female, white and bDMARD naïve.

Table 1: Select Baseline Patient Demographic and Disease Characteristics*	
Characteristic	**Full Analysis Set¥ (n = 505)**
Demographic Information	
Age, Years	59.3 (58.2, 60.4)
Duration Since RA diagnosis, Years (n = 490)ł	10.2 (9.3, 11.1)
Female, No. (%)	393 (77.8%)
White Race, No (%)	419 (83.0%)
Prior and Concomitant RA Medications, No. (%)	
bDMARD-Naive	299 (59.2%)
Concomitant csDMARDs $	333 (66.0%)
Concomitant Glucocorticoid Use	99 (19.6%)
Comorbidity Status, No (%)‡	
Chronic Pulmonary Disease/Asthma	77 (15.2%)
Coronary Artery Disease	5 (1.0%)
Diabetes	63 (12.5%)
Hypertension	121 (24.0%)
Malignancy**	34 (6.7%)
Myocardial Infarction	23 (4.6%)
Active Tuberculosis	3 (0.6%)
AIDS	4 (0.8%)
Disease Characteristics ŁŁ	
Clinical Disease Activity Index (n = 473)	29.4 (28.3, 30.5)

*Values are the mean (95% confidence interval) unless indicated otherwise.
¥ Defined as all enrolled patients providing consent to participate in the study and having started tofacitinib ≤28 days prior to baseline.
ł Calculated among patients with known duration since RA diagnosis.
$ Patients may have reported >1 concomitant csDMARD.
‡ Any prior history of chronic pulmonary disease/asthma, malignancy, myocardial infarction, and AIDS is reported.
**Includes preferred terms: basal cell carcinoma, breast cancer, cholangiocarcinoma, chondrosarcoma, colon cancer, endometrial adenocarcinoma, invasive ductal breast carcinoma, lip squamous cell carcinoma, lung neoplasm malignant, malignant melanoma, osteosarcoma, prostate cancer, renal cancer, skin cancer, squamous cell carcinoma of skin, and uterine leiomyoma. A given patient could have had more than one condition.
ŁŁ Calculated among patients with available data per routine care.

In total, 507 patients were included in the safety analysis set. Safety outcomes to month 36 are listed in Table 2 below. There was a total of 6 deaths reported in the study. The most frequent treatment-emergent adverse events were upper respiratory tract infection, hypertension, and urinary tract infection. Incidence density rates for treatment-emergent adverse events of special interest (HZ, MACE, Cancer and VTE) were infrequent.

Table 2: Safety Outcomes to Month 36*	
Patients with Event	**Safety Analysis Set¥ (n = 507)**
Treatment-Emergent Adverse Events	354 (69.8%) [129.5]
Serious Adverse Events	69 (13.6%) [11.46]
Study Discontinuations due to Adverse Events	95 (18.7%) [13.51]
Deaths	6 (1.2%) [1.02]
Most Frequent Treatment-Emergent Adverse Events (≥3%)	
Upper Respiratory Tract Infection	31 (6.1%) [3.86]
Hypertension	24 (4.7%) [2.72]
Urinary Tract Infection	23 (4.5%) [3.4]
Headache	22 (4.3%) [2.5]
Diarrhea	19 (3.7%) [2.16]
Pneumonia	17 (3.4%) [1.93]
Nausea	16 (3.2%) [1.93]
Treatment-Emergent Adverse Events of Special Interest	
Serious Infection	21 (4.1%) [2.95]
Herpes Zoster (Nonserious/Serious)$	13 (2.6%) [1.48]
Vaccinated	5 (2.2%) [1.17]
Unvaccinated	5 (2.5%) [1.5]
Major Adverse Cardiovascular Events	6 (1.2%) [0.68]
Malignancies (excluding Nonmelanoma Skin Cancer)**	14 (2.8%) [1.7]
Nonmelanoma Skin Cancer	4 (0.8%) [0.57]
Hepatic Events	9 (1.8%) [1.13]
Venous Thromboembolism	4 (0.8%) [0.57]
Deep Vein Thrombosis	2 (0.4%) [0.23]
Pulmonary Embolism	3 (0.6%) [0.34]
Gastrointestinal Perforation	0

* Values are the number of patients with events (%) [IDR]. IDR = Incidence density rate defined as the number of TEAEs over the sum of the length of time each patient at risk contributed to the study (expressed per 100 person -years).
¥ SAS is defined as all enrolled patients providing consent to participate in the study.
$ Vaccinated refers to patients receiving the herpes zoster (HZ) vaccine. Frequency and IDR of HZ in vaccinated and unvaccinated patients calculated in those patients with corresponding known vaccination status at baseline.
**Includes preferred terms: Acute myeloid leukemia, adenocarcinoma, bladder cancer, cholangiocarcinoma, malignant melanoma, malignant neoplasm progression, malignant pleural effusion, myeloproliferative neoplasm, neuroendocrine tumor, polycythemia vera, prostate cancer, small cell lung cancer metastatic, squamous cell carcinoma. A given patient could have had more than one condition.

Inclusion Criteria:

To be eligible for the study, patients had must have met each of the following inclusion criteria:

1. *Adult patients, at least 18 years of age or older at the time of recruitment.*
2. *Diagnosis with RA as per the revised 1987 American College of Rheum otology (ACR) criteria or 2010 ACR/EULAR criteria.*
3. *Patients for whom the treating physician has made the decision to commence tofacitinib treatment in accordance with the Canadian Product Monograph.*
4. *Initiation of treatment with tofacitinib within 28 days from study enrolment.*
5. *Acceptance for patients to participate in the study and the signing of the informed consent.*

Evidence of a signed and dated informed consent document indicating that the patient (or a legally acceptable representative) was informed of all relevant aspects of the study.

Exclusion Criteria:

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

1. *Patients who do not have the ability to answer the questionnaires by themselves or who have any kind of disorder that may affect their answers.*
2. *Patients diagnosed with autoimmune rheumatic diseases other than RA.*
3. *Cannot or will not sign informed consent.*
4. *Active participation or enrollment in an interventional trial.*
5. *Previous experience with tofacitinib through either a clinical trial or previous treatment.*
6. *Is not expected to be available for follow-up assessments as required for adequate management.*
7. *According to the judgment of the physician will not be able to participate in the study including the presence of any condition that, in the opinion of the treating physician, prohibits the patient from participating in the study or obscures the assessment of the treatment of RA.*
8. *Pregnant and breastfeeding women.*

9. *Patients with lymphoproliferative disorders (eg, Epstein Bass Virus (EBV) related lymphoproliferative disorder), have a history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.*

Results:

Interim results describing efficacy outcomes to month 18, including the coprimary outcomes of CDAI–defined LDA and REM (month 6), and safety to month 36 have been previously published.[24] An exploratory safety interim analysis was also conducted in patients aged ≥50 years with ≥1 CV risk factor; this abstract was first published at the ACR Convergence 2021 conference, and a future publication is planned.[24]

Below are the final results of this study representing a maximum follow-up period of 36 months from the initiation of treatment with tofacitinib; a future publication disseminating these final results is also planned. Of note, there was a protocol amendment in December 2020 to reduce the sample size from 800 patients (as originally targeted) to 500 patients, which was deemed adequate to fulfill the study's objectives.

There were 505 patients that initiated tofacitinib at baseline and that were included in the full analysis set. Baseline characteristics are shown in Table 1. The mean age at baseline was 59.3 years and the mean duration since rheumatoid arthritis diagnosis was 10.2 years. The majority of patients were also female, white and bDMARD naive.

Other Information:

Please note that discrepancies between the published interim analysis and the final analysis in this CSR are due to the fact that the investigators provided additional data in the 1.5 years that elapsed between the 2 analyses (ie, the database was not locked at the time of the interim analysis that informed the manuscript).

Portions of this study were conducted during the COVID-19 pandemic. As such, many clinical sites were closed to in-patient visits from March to December 2020. After December 2020, patients could continue with remote visits or present for in-clinic assessments. Specific details of issues reported by sites especially in 2020 may be found in Xeljanz_Covid Status_final.xlsx in Appendix 8.

Conclusion:

Overall, the results of this study indicate that tofacitinib provides early and sustained improvement of disease signs and symptoms in Canadian patients with RA, complementing other real-world data sets. The safety profile is consistent with previously published post marketing and clinical data. These results further substantiate the established tofacitinib safety profile, provide insight into expected effectiveness outcomes, and inform real-world outcomes for patients with RA.

Names and Affiliations of Principal Investigators:

Redacted

References

1. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001;358(9285):903-11.

2. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010;376(9746):1094-108.

3. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015. American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(1):1-26.

4. Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B, et al. Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. J Rheumatol. 2012;39(8):1559-82.

5. Singh JA, Hossain A, Tanjong Ghogomu E, Kotb A, Christensen R, Mudano AS, et al. Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: systematic review and network meta-analysis. Cochrane Database Syst Rev. 2016(5):CD012183.

6. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum. 2012;64(3):617-29.

7. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011(2):CD008794.

8. Barton J. L. Patient preferences and satisfaction in the treatment of rheumatoid arthritis with biologic therapy. Patient Prefer Adherence. 2009; 3:335-44.

9. Pfizer Canada Inc. XELJANZ Tofacitinib tablets. Product Monograph. 15 September 2015. Available at http://www.pfizer.ca/sites/g/files/g10028126/f/201511/Xeljanz_PM_E.pdf.

10. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Safety and efficacy of tofacitinib vs TNF inhibitors in RA patients aged 50 years or older with one or more cardiovascular risks: results from a Phase 3b/4 randomized safety trial. 2021; 73 (suppl 10).

11. Pfizer Canada ULC. XELJANZ/XELJANZ XR Tofacitinib tablets. Product Monograph. 9 December 2021. Available at http://www.pfizer.ca/xeljanz-tofacitinib.

12. Lundquist LM, Cole SW, Sikes ML. Efficacy and safety of tofacitinib for treatment of rheumatoid arthritis. World J Orthop. 2014;5(4):504-11.

13. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508-19.

14. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med. 2014;370(25):2377-86.

15. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2013;159(4):253-61.

16. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367(6):495-507.

17. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet. 2013;381(9865):451-60.

18. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: Twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum. 2013;65(3):559-70.

19. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23(2):137-45.

20. Pincus T, Yazici Y, Bergman MJ. RAPID3, an index to assess and monitor patients with rheumatoid arthritis, without formal joint counts: similar results to DAS28 and CDAI in clinical trials and clinical care. Rheum Dis Clin North Am. 2009;35(4):773-8, viii.

21. Prieto L, Sacristan JA. What is the value of social values? The uselessness of assessing health-related quality of life through preference measures. BMC Med Res Methodol. 2004; 4:10.

22. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11(3):570-9.

23. Wollenhaupt J, Silverfield J, Lee EB, Curtis JR, Wood SP, Soma K, et al. Safety and efficacy of tofacitinib, an oral janus kinase inhibitor, for the treatment of rheumatoid arthritis in an open-label, long-term extension studies. J Rheumatol. 2014;41(5):837-52.

24. Haraoui B, Khraishi M, Choquette D, Lisnevskaia L, Teo M, Kinch C, Galos C, Roy P, Gruben D, Woolcott JC, Vaillancourt J, Sampalis JS, Keystone EC; Canadian Tofacitinib for Rheumatoid Arthritis Observational Investigators. Effectiveness and Safety of Tofacitinib in Canadian Patients with Rheumatoid Arthritis: Primary Results from a Prospective Observational Study. Arthritis Care Res (Hoboken). 2023 Feb;75(2):240-251. doi: 10.1002/acr.24966. Epub 2022 Oct 10. PMID: 35678771.

25. Haraoui et al., Poster presentation at ACR 2021 congress (1674).