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REVIEW

Tofacitinib: Real-World Data and Treatment Persistence in Rheumatoid Arthritis

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Abstract: Tofacitinib is an oral Janus kinase (JAK) inhibitor indicated for the treatment of rheumatoid arthritis (RA). The efficacy and safety/tolerability of tofacitinib have been extensively evaluated as monotherapy and combination therapy in multiple, randomised, multicentre studies in patients with RA. Tofacitinib as monotherapy (as first- and second-line treatment) or as combination with methotrexate (MTX) or other csDMARDs as second- and third-line treatment is effective and generally well tolerated in patients with RA. This article focuses on recent real-world evidence investigating the effectiveness, treatment persistence and safety/tolerability of tofacitinib in patients with RA. With this purpose, a literature review was conducted from April 2018 up to October 2020 for the effectiveness, persistence and safety of tofacitinib for the treatment of RA, primarily focusing on real-world studies. These retrospective and prospective and observational studies demonstrate the effectiveness of tofacitinib, thus supporting pivotal data from the clinical trial programme. Treatment persistence was generally comparable to that of biologic disease-modifying anti-rheumatic drugs. Safety findings in these observational studies were consistent with the known safety profile of the approved dose of 5 mg twice daily.

Keywords: rheumatoid arthritis, real-world, effectiveness, persistence

Introduction

Recent EULAR recommendations for the management of rheumatoid arthritis (RA) state that following failure of 1 or more conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) and in the presence of at least one poor prognostic factor, a Janus kinase (JAK) inhibitor or a biological DMARD (bDMARD) should be started.[1] Tofacitinib is an oral JAK inhibitor for the treatment of RA. In cellular settings where JAKs signal in pairs, tofacitinib preferentially inhibits signalling by heterodimeric receptors associated with JAK1 and/or JAK3 and has functional selectivity over JAK2.[2,3]

The efficacy and safety/tolerability of tofacitinib have been extensively evaluated as monotherapy and combination therapy in multiple 6- to 24-month, randomised, double-blind, multicentre, Phase 3 or 3b/4 Oral Rheumatoid Arthritis (ORAL) studies in patients with RA. The findings from these controlled trials demonstrate that tofacitinib monotherapy (as first- and second-line treatment) and in combination with methotrexate (MTX) or other csDMARDs as second- and third-line treatment is effective and generally well tolerated in patients with RA.[4–11]

The open-label ORAL Sequel long-term extension study presented efficacy data for up to 8 years and safety data for up to 9.5 years on 4481 RA patients and a total tofacitinib exposure of 16,291 patient-years.[12] Tofacitinib maintained American

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College of Rheumatology-20% (ACR_{20}), −50% (ACR_{50}) and −70% (ACR_{70}) response rates between months 1 and 96, and efficacy was generally similar for 5 mg twice daily (BID) (months 1 to 96) and 10 mg BID (months 1 to 72). Tofacitinib (5 mg and 10 mg BID) reduced mean erythrocyte sedimentation rate (ESR)-based disease activity score assessed in 28 joints (DAS28-ESR) and improved mean Health Assessment Questionnaire Disability Index (HAQ-DI) scores at month 1; both DAS28-ESR and HAQ-DI scores remained stable during 96 months of treatment. Clinical Disease Activity Index (CDAI) and Simple Disease Activity Index (SDAI)-defined remission were obtained in about one-third of patients at month 96.

Tofacitinib administered as monotherapy or combination therapy showed a consistent safety profile.[12] The incidence rate for AEs leading to discontinuation was 6.8 patients per 100 patient-years. For all-cause AEs of special interest, the incidence rate was 3.4 per 100 patient-years for herpes zoster, and was lower for serious infections (2.4/100 patient-years), malignancies excluding non-melanoma skin cancer (NMSC; 0.8/100 patient-years), major adverse cardiovascular events (0.4/100 patient-years) and all-cause mortality (0.3/100 patient-years). Most all-cause AEs for tofacitinib were mild (59%) or moderate (36%) in severity, and proportions of mild and moderate all-cause AEs were similar for patients receiving tofacitinib 5 mg or 10 mg BID.

Observational studies and data collections from registries provide real-world evidence of therapies and complement randomised controlled trials (RCTs) as they provide invaluable information about routine clinical practice.[13–15] This review focuses on recent real-world evidence investigating the effectiveness, treatment persistence and safety/tolerability of tofacitinib in patients with RA, available since the review by Caporali & Zavaglia in 2019.[16]

Methods

For the purposes of this narrative review, PubMed was searched on 23rd October 2020 using the search terms "tofacitinib" and "rheumatoid arthritis" and limited to articles published from April 2018 up to October 2020. A total of 290 articles were assessed for relevance, focusing on real-world studies; long-term extension and economic studies were also found and evaluated if pertinent. Abstracts from ACR, European League Against Rheumatism (EULAR), and Asia Pacific League of Associations for Rheumatology (APLAR) meetings from 2018 to 2020 were also searched, since these often present the first reports and most up-to-date experience with drug therapy. The publications were subgrouped by those evaluating effectiveness and/or persistence and/or safety.

Results

Effectiveness and/or Persistence

Two real-world studies which analysed claims database or registry data reported only effectiveness outcomes.[17,18] Interrogation of US MarketScan® databases over a three-year period (2011–2014) showed similar effectiveness rates for tofacitinib and non-TNFi biologics. In a retrospective cohort analysis of MarketScan® databases involving 21,832 RA patients (0.8% receiving tofacitinib), six strict criteria were used to define effective therapy.[17] After one year, therapeutic effectiveness was 15.4% for tofacitinib, compared to 18.6% for TNFi, 19.8% for non-TNFi biologics and 11.1% for csDMARDs. Analysis of the US Corrona RA registry compared outcomes in patient cohorts receiving TNFi (n = 8014) or tofacitinib (n = 558) with/without MTX.[18] Effectiveness was assessed by CDAI-based low disease activity (LDA)/remission and modified ACR_{20} response rate. Tofacitinib as monotherapy or in combination achieved an efficacy similar to TNFi in combination with MTX in the third/fourth line, while association with MTX improved efficacy of TNFi in the second/third line.

Fourteen studies reported on the effectiveness and/or persistence of tofacitinib (Table 1). A retrospective study of US insurance claims databases compared patients who switched from adalimumab or etanercept to tofacitinib (n = 549) with those switching from adalimumab to etanercept or conversely from etanercept to adalimumab (n = 191).[19] Patients who switched from adalimumab to tofacitinib had significantly higher persistence (defined as persistence without a ≥60-day gap in index therapy or switch) and longer duration of therapy.

Thanks to the real-world collection in the US, information was obtained about two formulations of tofacitinib– modified-release (MR) 11 mg daily (QD) and immediate-release (IR) 5 mg twice daily (BID) – which were compared for effectiveness and adherence of patients initiating either product following interrogation of US claims databases (n = 1057) and the Corrona US RA Registry (n = 450)[20] (in 2016, in US, an extended-release dose of tofacitinib 11 mg once daily was approved). Assessed using clinical disease activity after 6 months of treatment, effectiveness was similar between the two formulations. Adherence was significantly higher with

Table 1 Patient Characteristics, Treatment Patterns and Outcomes in Real-World Studies with Tofacitinib

Study	Data Source	n	Design and Patients	Objectives	Tofacitinib Treatment	Main Findings	Treatment Persistence, Discontinuation and Adherence
Harnett et al 2019[19]	US-based IBM® MarketScan® Commercial and Medicare Supplemental insurance claims databases (January 2014 – September 2016)	740: switched from ADA or ETN to TOF (n=549); cycled between ADA and ETN (n=191)	Retrospective cohort study	Impact of TNFi cycling with ADA & ETN vs switching to TOF	NA	Patients switching from ADA/ETN to TOF had higher persistence, effectiveness, and significantly lower change in RA-related costs vs patients switching from ADA to ETN	Persistence rates: switching from ADA to TOF vs ADA to ETN, 50.5% vs 36.7% (p=0.03); from ETN to TOF vs ETN to ADA, 45.8% vs 38.4% (p=0.19).
							Mean (SD) duration of therapy: ADA to TOF vs ADA to ETN, 239.0 (134.5) vs 203.7 (133.2) days (p=0.04); ETN to TOF vs ETN to ADA, 234.3 (131.1) vs 219.8 (126.1) days (p=0.32)
Cohen et al 2020[20]	US IBM® MarketScan® Commercial and Medicare Supplemental insurance claims databases (March 2016–October 2018); Corrona US RA Registry (February 2016–August 2019)	US claims databases (n=1057); Corrona US RA Registry (n=450: MR 11 mg QD, n=297; IR 5 mg BID, n=153)	Retrospective, non-interventional cohort studies	Compare real-world adherence and effectiveness between patients initiating MR and IR formulations	TOF modified-release (MR) 11 mg QD vs immediate-release (IR) 5 mg BID	Effectiveness of TOF MR 11 mg QD was non-inferior to TOF IR 5 mg BID, assessed using two CDAI-based outcomes.	TOF MR 11 mg QD improved adherence.
							Adherence in TOF MR vs IR initiators:
							12-month ≥ 0.8 PDC: 48.2% vs 37.7% (p=0.001)
						Patients with CDAI improvement, TOF MR vs IR: 25.5% vs 22.1% (p=0.73)	12-month ≥ 0.8 MPR: 80.1% vs 69.9% (p=0.0002).
							12-month mean duration of treatment for TOF MR vs IR: 243.4 vs 235.7 days (p=0.36)
Fisher et al 2020[21]	Canadian IBM MarketScan Research Databases (November 2012 – December 2016)	New TOF users (n=1031); new bDMARD users (n=17,803)	Retrospective cohort study	Compare medication persistence of TOF vs injectable bDMARDs		New TOF users had shorter persistence compared with new bDMARD patients	Median persistence: TOF, 0.81 yr; bDMARDs, 1.02 yr.
							HR for discontinuation of TOF vs bDMARDs = 1.14 (95% CI: 1.05–1.25)

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Table 1 (Continued).

Study	Data Source	n	Design and Patients	Objectives	Tofacitinib Treatment	Main Findings	Treatment Persistence, Discontinuation and Adherence
Movahedi et al 2020[22]	Ontario Best Practices Research Initiative (OBRI) provincial registry, Canada	565 patients initiating TOF (n=208) or TNFi (n=357)	Retrospective cohort study	Discontinuation rates of TOF in comparison with TNFi, with/without concurrent MTX	NA	TOF retention in patients with/without MTX was similar	Discontinuation rates: TOF, 36% (n=75); TNFi, 29% (n=103) No significant difference in TOF discontinuation in patients with/without MTX (Logrank, p=0.31)
Pope et al 2020[23]	Canadian eXel programme (2014–2017)	4276 patients	Post hoc observational aggregated study	Describe characteristics, treatment patterns and persistence in RA patients treated with TOF	TOF 5mg BID, n=4092 (95.7%); 5 mg QD, n=184 (4.3%)	Increased use of TOF since 2014, especially among bDMARD-naïve/1-prior-bDMARD patients. Median persistence was ~2 years. Likelihood of persistence increased for bDMARD-naïve (vs bDMARD-experienced) patients and those aged ≥56 (vs ≤45) years.	Discontinuation rate for TOF (n=3678), 33.3%: due to ineffectiveness (35.7%), AEs (26.9%). Persistence: at 1 yr, 62.7%; at 2 yr, 49.6%
Tamura et al 2018[34]	Post-marketing surveillance in Japan	3929	Post-marketing interim analysis (first 6-month observation period) of 3-year follow-up	Rates of SAEs, malignancies, and deaths in Japanese RA patients receiving TOF [See Safety section below]		See Safety section (Table 2)	6-month discontinuation rate, 22.7%: due to AEs (8.9%), ineffectiveness (8.5%).
Mori & Ueki 2019[24]	Japanese single centre: NHO Kumamoto Saishunsou National Hospital (August 15, 2013 – August 15, 2017)	100	Prospective observational study	Compare outcomes of dose reduction, withdrawal, and restart of TOF in RA	TOF 5 mg, BID for 1 year	At 1-year: remission (53%), LDA (15%). Incidence rates (95% CI) of disease flare: after withdrawal, 0.73 per person-year (0.43–1.22); after dose reduction, 0.44 (0.25–0.77); during continuation 0.04 (0.01–0.27).	1-year discontinuation rate 32%: due to ineffectiveness (24%), AEs (4%), patient preference (4%)

Ebina et al 2020[26]	Kansai district, Japan Registry data (2001–2019)	3897 patients and 4415 treatment courses: ETN (856), TCZ (851), IFX (724), ABT (663), ADA (536), GOL (458), CZP (226), TOF (101).	Multicentre, retrospective ANSWER study	Assess retention rates and reasons for discontinuation for 7 bDMARDs and TOF in in bDMARD-naïve and bDMARD-switched RA patients	NA	Significant differences between agents for drug retention in bDMARD-naïve and bDMARD-switched patients	TOF drug discontinuation rates (bDMARD-switched patients): ineffectiveness, 22.8%; ADRs, 13.2%, non-ADR reasons, 7.7%; remission, 2.3%; all-causality AEs, 38.5%
Croiteru et al 2019[27]	Israeli RA registry (January 2010–February 2019)	864 treatment courses: TCZ (297), ETN (242), ABT (115), TOF (111), GOL (99)	Prospective cohort study	Real-life retention of TOF in RA		TCZ had longer drug persistence compared with TOF, ETN, ABT & GOL	TOF median drug persistence was 15.8 months (95% CI: 8.6–23.1) and non-inferior to ETN (26.4 months, 95% CI: 5.9–46.9; p=0.426), ABT (20.3 months, 95% CI: 9.8–30.9; p=0.157), and GOL (15.1 months, 95% CI: 5.9–24.3; p=0.698)
Mueller et al 2019[28]	Swiss St. Gallen & Aarau Cohorts (January 2015 – April 2017)	144	Retrospective cohort study	Assess the clinical tolerability and effectiveness of TOF	Initiated on TOF 5 mg BID	Mean DAS28 decreased significantly from 4.4 at baseline to 3.13 at 360 days. 53% achieved LDA & 48% DAS28-defined remission	Discontinuation rate during follow-up (mean 1.22 years), 38.2%: due to insufficient response (14.6%), AEs (23.6%)
Finckh et al 2020[29]	Swiss Clinical Quality Management in Rheumatoid Arthritis (SCQM-RA) Registry	2600 patients and 4023 treatment courses: TNFi (1862); bDMARDs-OMA (1355); TOF (806) initiators	Observational nested cohort study	Overall drug retention	TOF ≤5 mg bd (96.6%); >5–10 mg BID (3.4%) 47% monotherapy;53% combination with csDMARDs	TOF drug maintenance comparable with non-TNFi bDMARDs and significantly higher than TNFi	Overall drug maintenance: HR=1.29 (95% CI: 1.14–1.47) for TOF vs TNFi; HR=1.09 (95% CI: 0.96–1.24) for TOF vs non-TNFi bDMARDs
Zengin et al 2018[30]	Turkish nationwide TURKBIO registry	180	Cohort study in patients with RA	Investigate the persistence, effectiveness and safety of TOF in RA patients	NA	VAS pain scores, DAS28, HAQ & CRP significantly reduced from baseline to week 60	TOF persistence rates of 75% at 48 weeks and 48% at 137 weeks. Main reasons for drug discontinuation: ineffectiveness (63%), AEs (23%)

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Table 1 (Continued).

Study	Data Source	n	Design and Patients	Objectives	Tofacitinib Treatment	Main Findings	Treatment Persistence, Discontinuation and Adherence
Bilgin et al 2020[31]	Turkish single centre: Hacettepe University biological database (HUR-BİO)	Retention and safety (n=247), effectiveness (n=204)	Retrospective longitudinal study	Assess real-life effectiveness, retention rate and safety in RA patients receiving TOF	At last visit: monotherapy (± glucocorticoid), 16.6%; combination with ≥1 csDMARD, 83.4%	TOF effective as monotherapy or in combination with csDMARDs	1-year crude retention rate was 64%. Median duration of drug retention was 24.8 months
						Mean ± SD DAS28-ESR levels at baseline: 4.7 ± 1.4; and last visit (median 10.2 months) 3.6 ± 1.5	
Bird et al 2019; Bird et al 2020[32]	Australian Optimizing Patient outcomes in Australian RheumatoLogy (OPAL) dataset (March 2015 – September 2018)	1950 patients: propensity score-matched for treatment initiated with: bDMARDs (n=1300); TOF (n=650).	Retrospective, non-interventional cohort study	Evaluate treatment effectiveness and persistence	TOF monotherapy, 43.4%	TOF and bDMARDs had similar treatment effectiveness and persistence.	Median treatment persistence: TOF, 34.2 months (95% CI: 32.2–not reached); bDMARDs, 33.8 months (95% CI: 28.8–40.4)
						DAS28-ESR remission rates at 18 months: TOF, 57.8%; bDMARDs, 52.4%.	
						CDAI remission at 18 months: TOF, 30.9%; bDMARDs, 29.0%;	
						SDAI remission at 18 months: TOF, 30.5%; bDMARDs, 29.2%	

Abbreviations: ABT, abatacept; ADA, adalimumab; AE, adverse event; bDMARDs, biologic DMARDs; BID, twice daily; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; CZP, certolizumab pegol; CI, confidence interval; csDMARDs, conventional synthetic DMARDs; DAS, disease activity score; DAS28-ESR, disease activity score in 28 joints using erythrocyte sedimentation rate; ETN, etanercept; GLM, golimumab; HAQ, Health Assessment Questionnaire; IFX, infliximab; HR, hazard ratio; LDA, low disease activity; MCID, minimum clinically important difference; MPR, medication possession ratio; MTX, methotrexate; NA, not applicable; OR, odds ratio; QD, once daily; PDC, proportion of days covered; RTX, rituximab; SD, standard deviation; SDAI, Simplified Disease Activity Index; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib.

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tofacitinib MR compared with the IR formulation. Duration of treatment was comparable for both formulations.

A Canadian study of IBM MarketScan Research databases with data from the US found that new tofacitinib users (n = 1031) had shorter medication persistence compared to new bDMARD patients (n = 17,803).[21] Median persistence was 0.81 vs 1.02 years, respectively, and the adjusted hazard ratio (HR) for discontinuation of tofacitinib compared with bDMARDs was 1.14 (95% CI: 1.05–1.25). However, patients who switched from a bDMARD to tofacitinib had longer persistence than those who switched from one bDMARD to another agent: adjusted HR for discontinuation was 0.90 (95% CI: 0.83–0.97).

A Canadian study from the Ontario Best Practices Research Initiative (OBRI) in patients initiating tofacitinib (n = 208) or TNFi (n = 357), reported discontinuation rates of 36% and 29%, respectively, during a mean follow-up of 17.3 months.[22] Discontinuation rates in patients receiving tofacitinib monotherapy or in combination with MTX were similar.

Data from the Canadian eXel programme reported a discontinuation rate for tofacitinib initiators (n = 3678) of 33.3%, which was due to ineffectiveness in 35.7% of cases, adverse events (AEs) in 26.9%, and patient decision to try another therapy in 12.0% of cases.[23] Temporary cessation was observed in 7.7% of patients. Persistence rates at 1 and 2 years were 62.7% and 49.6%, respectively (defined as percentage of patients remaining on tofacitinib after receiving ≤1 dose). Median drug survival in bDMARD-naïve, post-1 bDMARD, post-2 bDMARD and post-≥3 bDMARD patients, was >730, 613, 667 and 592 days, respectively. An increased likelihood of tofacitinib persistence was associated with bDMARD-naïvity (vs bDMARD-experienced; $p < 0.001$), increased aged (≥56 vs ≤45 years; $p < 0.05$) and time since diagnosis of 15–19 years (vs <5 years; $p < 0.01$).

A single centre Japanese study of RA patients (n = 100) found that after year 1 of tofacitinib treatment, 53% achieved remission and a further 15% had low disease activity (CDAI < 2.8 and ≤ 10). The 1-year discontinuation rate was 32% (ineffectiveness 24%, AEs 4% and patient preference 4%).[24] Interim analysis of post-marketing surveillance of tofacitinib in Japan reported that during the first 6 months of study, 22.7% of all patients (n = 3929) discontinued treatment mainly due to AEs (8.9%) and lack of efficacy (8.5%).[25]

The Japanese ANSWER retrospective study of registry data compared drug retention for 7 bDMARDs and tofacitinib in biologic-naïve and biologic-experienced RA patients.[26] For tofacitinib, data were available for 101 patients who were switched from a bDMARD. Drug discontinuation rates due to lack of effectiveness differed significantly between the 8 agents in bDMARD-switched patients ($p < 0.001$), ranging from relatively low values for tocilizumab (18.9%) and tofacitinib (22.8%) to 46.1% for certolizumab pegol. Drug discontinuation rates due to remission were comparable and ranged from 1.1% for certolizumab pegol to 3.3% for golimumab, and with 2.3% for tofacitinib.

Analysis of Israeli RA registry data on 864 treatment courses compared persistence for four bDMARDs and tofacitinib.[27] Median drug persistence for tofacitinib was 15.8 months (95% CI: 8.6–23.1) and was non-inferior to etanercept (26.4 months, 95% CI: 5.9–46.9; $p = 0.426$), abatacept (20.3 months, 95% CI: 9.8–30.9; $p = 0.157$) and golimumab (15.1 months, 95% CI: 5.9–24.3; $p = 0.698$). Compared with tofacitinib, etanercept, abatacept and golimumab, tocilizumab had a significantly higher retention rate (HR for drug survival vs tofacitinib was 1.92, 95% CI: 1.33–2.76), but tofacitinib was mostly prescribed as third or later line of therapy (64%)

A Swiss retrospective study of the St. Gallen and Aarau Cohorts assessed tolerability and effectiveness in patients initiated on tofacitinib (n = 144).[28] Tofacitinib significantly reduced mean DAS28 from 4.4 at baseline to 3.13 at 360 days; 53% of patients achieved LDA and 48% DAS28-defined remission. The rates of LDA and remission for tofacitinib were higher in biologic-naïve patients compared to those who had previous biologic exposure: 100% of biologic-naïve patients achieved LDA, and 83.3% achieved remission, compared with 53.3% and 44.9% of patients pre-exposed to biologics. The discontinuation rate during a mean of 1.22 years follow-up was 38.2% which was attributable to AEs (23.6%) and insufficient response (14.6%).

Analysis of the Swiss Clinical Quality Management in Rheumatoid Arthritis (SCQM-RA) Registry found that drug maintenance in tofacitinib initiators (n = 806) was significantly higher than TNFi initiators (n = 1862) and comparable with non-TNFi bDMARDs (eg, rituximab, tocilizumab, abatacept) initiators (n = 1355). Median (IQR) drug maintenance was 25 months (19–30) for tofacitinib, 19 months (17–22) for non-TNFi bDMARDs and 17 months (15–18) for TNFi. The adjusted HR for drug discontinuation with TNFi compared with tofacitinib was 1.29 (95% CI: 1.14–1.47) and was 1.09 (95% CI: 0.96–

1.24) for both non-TNFi bDMARDs and tofacitinib. Discontinuation was most commonly due to ineffectiveness with lower rates for tofacitinib (46%) compared with non-TNFi bDMARDs (50%) and TNFi (57%).[29]

A retrospective analysis of RA patients (n = 180) in the Turkish nationwide TURKBIO registry showed that tofacitinib significantly reduced VAS pain scores, DAS28, HAQ and C-reactive protein (CRP) from baseline to week 60.[30] Tofacitinib persistence rates were 75% at 48 weeks and 48% at 137 weeks. The main reasons for tofacitinib discontinuation were ineffectiveness (63%) and AEs (23%). In a Turkish single centre study (n = 204), tofacitinib reduced mean ± SD DAS28-ESR levels from 4.7 ± 1.4 at baseline to 3.6 ± 1.5 at last visit (median 10.2 months); tofacitinib had a 1-year crude retention rate of 64% and a median duration of drug retention of 24.8 months.[31]

Analysis of the Australian Optimizing Patient outcomes in Australian RheumatoLogy (OPAL) dataset used propensity score matching at a ratio of 1:2 to compare with tofacitinib (n = 650) and bDMARDs (n = 1300).[32] Similar DAS remission rates at 18 months were reported for tofacitinib (57.8%) and bDMARDs (52.4%) and the proportion of patients achieving CDAI or SDAI remission was similar with respective rates of 30.9% and 30.5% for tofacitinib, and 29.2% and 29.0% for bDMARDs. Median treatment persistence was similar for tofacitinib (34.2 months; 95% CI: 32.2–not reached) and bDMARDs (33.8 months; 95% CI: 28.8–40.4).

Safety

Results from real-world studies on the safety and tolerability of tofacitinib are summarised in Table 2. A prospective, observational study of US Corrona RA registry data evaluated 5-year AE incidence rates in propensity score trimmed tofacitinib (n = 1117) and bDMARD (n = 5542) initiators.[33] The most common AEs in an interim analysis (first 6-month observation period) of a 3-year study post-marketing surveillance of tofacitinib (n = 3929) in Japan were herpes zoster (3.7%) and abnormal hepatic function (1.8%). Serious AEs were reported in 287 patients (7.3%), commonly herpes zoster (0.6%) and pneumonia/bacterial pneumonia (0.8%).[34] A retrospective study of Swiss Cohorts (n = 144) found a discontinuation rate due to AEs of 23.6% which was comparable to that reported in the ORAL Sequel LTE study (25%).[12] Gastrointestinal symptoms (12.5%) were the main reason for stopping treatment in the Swiss Cohorts.[28] A retrospective Turkish single centre study found that tofacitinib was well tolerated and had a discontinuation rate due to AEs of 15.0%, most commonly due to allergic skin reactions (2.4%). The most common infectious and laboratory AEs were herpes zoster (3.9 per 100 patient-years) and ALT elevation (9.7 per 100 patient-years), respectively.[31]

Thrombosis/Cardiovascular Disease (CVD)

Retrospective analysis of the US FORWARD database spanning 20 years, which included 17,363 RA patients, compared the CVD risk with biologics and tofacitinib to csDMARDs.[35] The study found a significant reduction in CVD risk with TNFi and abatacept, a non-significant reduction with tofacitinib and a significant increase with glucocorticoids. Adjusted HRs for CVD vs csDMARDs were: TNFi, 0.79 (95% CI: 0.69–0.92), abatacept, 0.53 (95% CI: 0.30–0.92); tofacitinib, 0.33 (95% CI: 0.05–2.38); rituximab, 0.78 (95% CI: 0.41–1.47); tocilizumab, 1.00 (95% CI: 0.44–2.27); anakinra, 0.87 (95% CI: 0.32–2.33); and glucocorticoids, 1.15 (95% CI: 1.11–1.20).

In the US Corrona RA registry, incidence rates of MACE and VTE were comparable for tofacitinib and bDMARDs initiators.[33] This prospective, observational, 5-year analysis examined data from 1544 initiators of tofacitinib (2138 patient-years) and 7083 bDMARD (9905 patient-years) initiators. The adjusted HR for MACE for both cohorts was 0.60 (95% CI: 0.30–1.18). Rates of VTE were also similar between tofacitinib and bDMARDs.

Analysis of US Marketscan claims databases found comparable risks for VTE in patients initiating treatment with tofacitinib (n = 2155) or adalimumab (n = 6022).[36] After a median follow-up of 0.5 years, the VTE incidence rate for tofacitinib was 1.31 per 100 patient-years (95% CI: 0.80–2.03) and for adalimumab was 0.83 per 100 patient-years (95% CI: 0.60–1.14).[36]

Analysis of US Truven MarketScan (n = 34,074) and Medicare claims (n = 17,086) databases found no significant difference in the risk of VTE between tofacitinib-treated and TNFi-treated patients.[37] The crude incidence rate of VTE in the Truven database for tofacitinib was 0.60 per 100 person-years (95% CI: 0.26–1.19) and for TNFi was 0.34 (95% CI: 0.27–0.41); in the Medicare database it was 1.12 (95% CI: 0.45–2.31) and 0.92 (95% CI: 0.76–1.11), respectively.[37]

Table 2 Real-World Studies with Tofacitinib: Safety

Study	Data Source	N	Design and Patients	Objectives	Main Findings	Discontinuation Rate Due to AEs
Kremer et al 2019[33]	US Corrona RA registry	1544 TOF & 7083 bDMARD starters. After propensity score-matching: 1117 TOF & 5542 bDMARD starters	Prospective, observational 5-year study	Evaluate 5-year AE incidence rates (IRs) in new starters of TOF vs bDMARDs	Patients starting TOF or bDMARDs had similar MACE, SIE, and VTE rates. TOF starters had higher HZ IRs vs bDMARD starters.	NA
Tamura et al 2018[34]	Post-marketing surveillance in Japan	3929	Post-marketing interim analysis (first 6-month observation period) of 3-year follow-up	Rates of SAEs, malignancies, and deaths in Japanese RA patients receiving TOF.	SAEs in 7.3% of patients: commonly herpes zoster (0.6%) and pneumonia/bacterial pneumonia (0.8%). See Malignancy section below for cancer rates	NA
Mueller et al 2019[28]	Swiss St. Gallen & Aarau Cohorts (January 2015 – April 2017)	144	Retrospective	Assess the clinical tolerability and effectiveness of TOF	TOF was safe with an AE discontinuation rate comparable with LTE studies	AE discontinuation rate 23.6%: GI symptoms (12.5%), infection (3.5%), myalgia (1.4%), headache (1.4%), cough, blue finger syndrome, intolerance, heartburn, psoriasis, and increased liver enzymes (all 0.7%)
Bilgin et al 2020[31]	Turkish single centre: Hacettepe University biological HUR-BİO database	Retention and safety (n=247)	Retrospective longitudinal study	Assess real-life effectiveness, retention rate and safety in RA patients receiving TOF	TOF was well-tolerated. Most common infectious AE was herpes zoster (3.9 per 100 patient-years) and laboratory AE was ALT elevation (9.7 per 100 patient-years)	TOF discontinuation rate due to AEs, 15.0%, most commonly allergic skin reaction (2.4%)
Cardiovascular disease (CVD)						
Ozen et al 2018[35]	US FORWARD database - The National Databank for Rheumatic Diseases, (1998–2017)	17,363	Retrospective	Compare effects of bDMARDs and TOF vs csDMARDs on incident CVD in RA patients	Significant CVD risk reduction with TNFi and ABT compared with csDMARDs. Adjusted HR (95% CI) for CVD vs csDMARDs: TNFi, 0.79 (0.69–0.92), ABT, 0.53 (0.30–0.92); TOF, 0.33 (0.05–2.38); RTX, 0.78 (0.41–1.47); TCZ, 1.00 (0.44–2.27); anakinra, 0.87 (0.32–2.33).	

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Table 2 (Continued).

Study	Data Source	N	Design and Patients	Objectives	Main Findings	Discontinuation Rate Due to AEs
Yun et al 2018[36]	US Marketscan claims databases (2010–2015)	TOF (n=2155) and adalimumab (n=6022) initiators	Retrospective cohort study	Evaluate risk of VTE (composite of PE or DVT) in RA patients initiating TOF or adalimumab	Comparable risk for VTE in patients treated with TOF or adalimumab. VTE incidence rates: TOF, 1.31 per 100 patient-years (95% CI: 0.80–2.03); adalimumab, 0.83 (95% CI: 0.60–1.14)	
Desai et al 2019[37]	US Truven MarketScan database (2012–2016), Medicare claims database (2012–2015)	51,160: 34,074 (Truven), 17,086 (Medicare)	Retrospective cohort study	Evaluate risk of VTE in RA patients receiving TOF versus TNF inhibitors	No significant difference in risk of VTE between TOF- and TNFi-treated patients.	
Mease et al 2020[38]	US Corrona registry, IBM MarketScan research databases, US FDA Adverse Event Reporting System (FAERS) database.	Corrona RA registry: bDMARD initiators (n=5159), TOF initiators (n=1130); MarketScan database for RA: all bDMARD initiators (n=47,496), TOF (n=5521); TOF FAERS data: 1210 unique reports	Retrospective real-world database analysis	Venous and arterial thromboembolic events in TOF RA, PsO & PsA real-world data	VTE and ATE incidence rates comparable for bDMARD and TOF initiators. Corrona RA registry: incidence rates (95% CI) for VTE: bDMARD initiators 0.32 (0.20–0.47), TOF initiators 0.18 (0.04–0.51) MarketScan database for RA: incidence rates (95% CI) for VTE: bDMARD initiators, 0.94 (0.85–1.03); TOF, 1.05 (0.78–1.39); for ATE: bDMARD initiators, 0.04 (0.03–0.07); TOF, 0.04 (0.00–0.17)	
Infectious diseases						
Machado et al 2018[17]	US MarketScan® databases (01/01/11–31/12/14)	21,832 patients treated with: TOF (164); non-TNFi biologics (2902); TNFi therapy (13,367); other DMARDs (5399)	Retrospective cohort study of adults with RA previously treated with MTX	Study of effectiveness and safety of MTX-exposed patients with RA, newly prescribed with: TOF, other DMARDs (not MTX), or biologics	Similar hospitalised infection rates for TOF ± DMARDs, DMARDs and TNFi ± DMARDs. Rates of serious infections: TOF ± DMARDs, 3.67 per 100 patient-years (95% CI: 2.21–5.75); DMARDs, 2.01 (95% CI: 1.65–2.42); TNFi ± DMARDs, 2.16 (95% CI: 1.98–2.36)	NA

Curtis et al 2019[39]	US MarketScan and Medicare databases (2011–2016)	8030 new TOF users	Retrospective cohort study	Evaluated herpes zoster risk in TOF users with / without MTX & glucocorticoids	Herpes zoster infection rate approximately 4% per year in TOF users	
Pawar et al 2020[40]	US Medicare (2012–2015), Optum Clinformatics (2012–2018) and IBM MarketScan (2012–2017) databases	130,718	Retrospective multi-database cohort study	Compared risk of serious infection in RA patients initiating TOF or other bDMARDs	Serious infection risk with TOF was significantly higher than etanercept, significantly lower than infliximab and non-significantly higher than ABT, GOL, and TCZ. TOF was associated with a 2-fold higher risk of herpes zoster vs all bDMARDs.	
Winthrop et al 2021[41]	US Corrona RA registry	Registry data set (n = 10,357): TOF, (n=1999), bDMARD (n=8358).	Retrospective cohort study	Assessed age-based (<65 vs ≥65 years) SIE risk in RA patients receiving TOF or bDMARD initiators	SIE incidence was higher in older vs younger patients in both TOF initiators and bDMARD initiators. SIE incidence similar between TOF and bDMARD initiators for both age groups. Incidence rates (95% CI) of SIEs in the Corrona RA registry: aged <65 years: TOF initiators, 1.89 (1.34–2.59); bDMARD initiators, 2.20 (1.88–2.56) Aged ≥65 years: TOF initiators, 5.32 (4.02–6.91); bDMARD initiators 4.20 (3.62–4.86)	
Tamura et al 2018[25]	Post-Marketing Surveillance in Japan	3929	Interim analysis (first 6-month observation period) of 3 year surveillance	Incidence of SIEs in Japanese RA patients treated with TOF	At month 6, SIEs in 130 (3.3%) patients: herpes zoster (n=24; 0.6%), pneumonia (n=23; 0.6%), *Pneumocystis jiroveci* pneumonia (n=15; 0.4%), bacterial pneumonia (n=10; 0.3%).	
Bilgin et al 2020[31]	HURBIO Registry, Turkey	204	Retrospective longitudinal study	Assessed the real-life incidence of herpes zoster in RA patients receiving TOF	Herpes zoster incidence rate, 3.9 (95% CI: 2.3–8.5) per 100 patient-years	

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Table 2 (Continued).

Study	Data Source	N	Design and Patients	Objectives	Main Findings	Discontinuation Rate Due to AEs
Malignancy						
Tamura et al 2018[34]	Post-marketing surveillance in Japan	3929	Post-marketing interim analysis (first 6-month observation period) of 3-year follow-up	Rates of SAEs, malignancies, and deaths in Japanese RA patients receiving TOF.	All-causality malignancy in 0.6% (n=25); 0.3% (n=12) reported to be treatment-related.	
Kremer et al 2019[42]	US Corrona RA registry (Nov 6, 2012 – July 31, 2018)	TOF (n=1999) and bDMARD (n=6354) initiators	Patients propensity score-matched for total cancer (excluding NMSC), NMSC, and death	Compared 5-year incidence rates for SAEs & AEs of interest in patients starting TOF vs bDMARDs	RA patients initiating TOF or bDMARDs had similar rates of total cancer excluding NMSC, NMSC, and death	
Xie et al 2020[43]	Meta-analysis of 10 observational studies	42,168 patients and >87,622 patient-years of exposure to non-TNFi biologics; 2221 patients with >4506 patient-years of exposure to TOF	Meta-analysis of real-world data	Assessed risk of developing cancer in RA patients exposed to non-TNFi biologics or TOF therapy	No increased risk of developing cancer overall or in specific cancer types in RA patients receiving TOF compared with csDMARDs or TNFi	

Abbreviations: ADRs, adverse drug reactions; AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATE, arterial thromboembolism; bDMARDs, biologic DMARDs; CI, confidence interval; CRP, C-Reactive Protein; csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying anti-rheumatic drugs; DVT, deep vein thrombosis; GI, gastrointestinal; HR, hazard ratio; LDA, low disease activity; MACE, major adverse cardiovascular events; MTX, methotrexate; NA, not available; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; PsA, psoriatic arthritis; PsO, psoriasis; RR, relative risk; SAE, serious adverse event; SIE, serious infection event; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib; VTE, venous thromboembolism.

Mease et al 2020 reported observational data from the US Corrona registries (including cardiovascular risk factor stratification), IBM MarketScan research databases and the US FDA Adverse Event Reporting System (FAERS) database as well as results from separate RA, psoriasis (PsO) and psoriatic arthritis (PsA) development programmes for tofacitinib 5 mg vs 10 mg BID.[38] Incidence rates of deep vein thrombosis (DVT), pulmonary embolism (PE) and arterial thromboembolism (ATE) in the tofacitinib RA, PsO and PsA programmes were similar across tofacitinib doses, and were generally consistent with the real-world data. In the Corrona RA registry, the VTE incidence rate for bDMARD initiators was 0.32 per 100 patient-years' exposure (95% CI: 0.20–0.47) and 0.18 (95% CI: 0.04–0.51) for tofacitinib initiators. In the MarketScan databases for RA, incidence rates of VTE were 0.94 (95% CI: 0.85–1.03) and 1.05 (95% CI: 0.78–1.39), respectively. Respective incidence rates for ATE were 0.04 (95% CI: 0.03–0.07) and 0.04 (95% CI: 0.00–0.17), respectively.[38]

Infections

Retrospective analysis of US MarketScan® databases of adults with RA previously treated with MTX (n = 21,832) found similar hospitalised infection rates for tofacitinib ± DMARDs, DMARDs and TNFi ± DMARDs.[17] Rates of serious infections were: tofacitinib ± DMARDs, 3.67 per 100 patient-years (95% CI: 2.21–5.75); DMARDs, 2.01 (95% CI: 1.65–2.42); and TNFi ± DMARDs, 2.16 (95% CI: 1.98–2.36).

Retrospective analysis of US MarketScan and Medicare databases of new users of tofacitinib (n = 8030) with or without MTX and glucocorticoids estimated the herpes zoster infection rate as approximately 4% per year.[39]

Analysis of multiple databases in the US reported that serious infection risk with tofacitinib was significantly higher than with etanercept, significantly lower than with infliximab, non-significantly higher than with abatacept, golimumab and tocilizumab, and similar to adalimumab and certolizumab.[40] Adjusted HRs for serious infection for tofacitinib vs bDMARDs were: vs etanercept, 1.41 (95% CI 1.15–1.73); vs infliximab, 0.81 (95% CI: 0.65–1.00) vs abatacept, 1.20 (95% CI: 0.97–1.49); vs golimumab, 1.23 (95% CI: 0.94–1.62); tocilizumab, 1.17 (95% CI: 0.89–1.53); vs adalimumab, 1.06 (0.87–1.30); vs certolizumab pegol, 1.02 (95% CI: 0.80–1.29).

In the US Corrona RA registry, the adjusted HR for SIEs was 0.99 (95% CI: 0.72–1.36), and tofacitinib initiators had higher rates of herpes zoster compared with bDMARD initiators for a significantly increased adjusted HR (2.12; 95% CI: 1.22–3.66).[33] All herpes zoster events with tofacitinib were non-serious. When stratified by age (<65 vs ≥65 years), the incidence of serious infections with tofacitinib vs bDMARDs was higher in older patients for both tofacitinib initiators and bDMARD initiators and similar between tofacitinib and bDMARD initiators for both age groups.[41]

All-case post-marketing surveillance in Japanese patients with RA treated with tofacitinib reported that 6-month serious infection events occurred in 130 (3.3%) patients, most commonly herpes zoster (0.6%) and pneumonia (0.6%).[25]

Assessment of the risk for herpes zoster in tofacitinib-treated RA patients, with or without concomitant methotrexate and glucocorticoids, reported an infection rate of approximately 4% per year.[39]

Malignancy

The prospective, observational, 5-year analysis of the US Corrona RA registry examined data from 1999 patients initiating tofacitinib (4505.62 patient-years) and 6354 initiating a bDMARD (16,670.84 patient-years).[42] In the entire population, HRs were: for total cancer (excluding NMSC), 1.04 (95% CI: 0.68–1.61); NMSC, 1.02 (95% CI: 0.69–1.50); and death, 1.0 (95% CI: 0.62–1.63).[42] Similar rates of all cancers (excluding NMSC), NMSC and death were seen for tofacitinib and bDMARDs.[42]

Interim (6-month) post-marketing surveillance of malignancy in Japanese RA patients treated with tofacitinib reported all-causality malignancy in 25 patients (0.6%), of which 12 were considered to be treatment-related.[34] A total of 21 deaths (0.5%) occurred during the 6-month period, most commonly due to infection (n = 6; 0.15%) and malignancy (n = 5; 0.13%). Over 36 months, malignancy was reported in 61 patients (4874 patient-years) with a cumulative incidence rate of 1.25/100 patient-years. Rates of malignancies and death were comparable with those in the tofacitinib RA clinical programme and no new or unexpected safety risks were identified.

A meta-analysis of observational studies assessed the risk of malignancy with non-TNFi biologic or tofacitinib therapy in RA.[43] The analysis, including 10 studies and involving 42,168 patients and >87,622 patient-years of exposure to non-TNFi biologics, included 2221 patients with >4506 patient-years of exposure to tofacitinib. There was no increased risk of developing cancer overall or in

specific cancer types in RA patients receiving tofacitinib compared with those receiving csDMARDs or TNFi.

Discussion

Drug retention rates may differ markedly between different bDMARDs.[44–48] Several factors affecting bDMARD drug retention rates have been reported, although some appear to be drug- or drug class-specific. For tofacitinib, bDMARD-naïvity (compared with prior bDMARD experience), older age (≥56 vs ≤45 years) and longer time since diagnosis (15–19 vs <5 years) significantly increased the likelihood of drug retention in a study from Canada,[23] but these findings wait further confirmation. Future real-world studies may delineate other predictors of tofacitinib drug retention.

Discontinuation rates due to ineffectiveness were slightly lower with tofacitinib (46%) than non-TNFi bDMARDs (50%) and TNFi (57%), but rates due to intolerance or AEs were comparatively higher with tofacitinib: 30% versus 22% and 19%, respectively. In these analyses of Swiss Registry data, median drug maintenance was longer for tofacitinib (25 months), than non-TNFi bDMARDs (19 months) and TNFi (17 months).[29] In contrast, a retrospective, non-interventional cohort analysis of the Australian OPAL dataset (derived from 42 rheumatology clinics in Australia, collecting information from individual clinicians' servers during routine clinical consultations) reported similar median treatment persistence of approximately 34 months for tofacitinib compared with bDMARDs.[32] A previous review of real-world studies (up to mid-2018) found that treatment persistence and adherence to tofacitinib was good overall and similar to those seen for bDMARDs.[16] RA patients initiating tofacitinib usually had longer disease duration and had been exposed to longer bDMARDs than patients initiating a bDMARD. Real-world data demonstrate the value of monotherapy with tofacitinib, showing the drug retention rate is not affected when in association with MTX, differently than bDMARDs,[22] and the effectiveness of tofacitinib as monotherapy appears similar to tofacitinib in combination therapy, in contrast to anti-TNF agents.[18]

There is growing evidence of the safety of JAK inhibitors in patients with RA.[49] Evaluation of the risks of relatively rare serious AEs such as VTE, gastrointestinal perforation and interstitial lung disease in clinical practice requires the accumulation of cases with these events. Continuous pharmacovigilance activity is essential to establish the safety of JAK inhibitors in patients with RA and other rheumatic diseases.[49]

Patients with RA have increased risk of CVD. Observational studies suggest that in the general population and non-RA controls, there are 0.1–0.4 thromboembolic events per 100 patient-years. In RA, thromboembolic risks increase to 0.3–0.7 per 100 patient-years.[50,51] Interestingly, a recent meta-analysis of patients with immune-mediated inflammatory diseases (n = 13,611) enrolled in RCTs (n = 29) found that tofacitinib had analogous rates of all cardiovascular events (odds ratio [OR] = 1.07, 95% CI: 0.49–2.34), MACE (OR = 1.54, 95% CI: 0.42–5.59) and all-cause mortality (OR = 1.13, 95% CI: 0.26–4.95) compared with placebo, but a decreased rate of VTEs (OR = 0.03, 95% CI: 0.00–0.21).[52] Similarly, a meta-analysis of patients with immune-mediated inflammatory diseases enrolled in RCTs (n = 42) reported no increased risk of VTE for JAK inhibitors as a group (6542 patient exposure years) compared with placebo (1578 patient exposure years).[53] Data pooled from six phase 3 and two long-term extension studies of tofacitinib in RA patients over 7 years, identified 52 MACE occurring in 4076 patients during 12,873 patient-years of exposure for an incidence rate of 0.4 per 100 patient-years.[54] Additionally, a systematic literature review on 33 clinical trials, 39 prospective and 18 retrospective real-world studies, concluded that there were no indications of a significant increase in adverse cardiovascular events for bDMARDs and tofacitinib in patients with rheumatic diseases.[55]

Importantly, data from a recently completed large randomized prospective post-authorization safety study comparing tofacitinib with anti-TNF therapy in patients with RA who were aged ≥50 years and had ≥1 additional CV risk factor showed an increased rate for tofacitinib relative to anti-TNF therapy regarding venous thromboembolic events (VTE) and major adverse cardiovascular events.[56,57] Given that the underlying mechanism(s) for these adverse events remain unknown, the effect of JAK inhibitors on CVD risk requires further research.

The utility of real-world evidence for informing healthcare policymakers when making appropriate decisions about treatment pathways has been recognised.[58] This review of tofacitinib considering recent real-world evidence provides an update from a previous review which included studies up to mid-2018.[16] These retrospective and prospective observational studies have demonstrated the effectiveness of tofacitinib and reinforce data from the pivotal clinical trial programme. Treatment persistence was generally comparable to that of bDMARDs, and the

safety findings in these observational studies were consistent with the known safety profile of the approved dose of 5 mg BID.

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