Review

Real-world experience with tofacitinib for the treatment of rheumatoid arthritis

R. Caporali[1], D. Zavaglia[2]

[1]Division of Rheumatology, University of Pavia, IRCCS S. Matteo Foundation, Pavia, Italy; [2]Medical Department, Pfizer Italy, Rome, Italy

Roberto Caporali, MD
Daniela Zavaglia, MD

Please address correspondence and reprint requests to:
Dr Roberto Caporali,
Division of Rheumatology, IRCCS S. Matteo Foundation,
Piazzale Golgi 2,
27100 Pavia, Italy.
E-mail: caporali@smatteo.pv.it

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ABSTRACT

Objective. *Oral targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs), including the Janus kinase inhibitors tofacitinib and baricitinib, are the latest addition to the therapeutic options for rheumatoid arthritis (RA). Tofacitinib 5 mg, twice daily, is approved for treatment, with or without methotrexate, of moderate to severe active RA in adults not adequately responding to, or not tolerating one or more DMARDs. In this narrative review we aimed to provide an overview of the real-world evidence for tofacitinib in RA.*

Methods. *The literature was reviewed up to March 2018 for studies regarding the efficacy and safety of tofacitinib for the treatment of RA. The focus was mainly on real-world studies with implications for every day clinical practice.*

Results. *The efficacy and safety of tofacitinib have been comprehensively assessed in a wide programme of randomised controlled trials. Extensive observational research on tofacitinib in RA is also ongoing worldwide and a substantial body of post-marketing real-world data from clinical practice is becoming available. There was a degree of consistency across the real-world studies reviewed. Tofacitinib tends to be used as monotherapy more frequently than bDMARDS and appears to be effective without background methotrexate. The data show a manageable safety profile, with no new safety signals and a discontinuation rate from safety issues <10%. Patients initiating tofacitinib usually have longer disease duration and have been exposed to longer bDMARDs than patients initiating a bDMARD.*

Conclusion. *Real-world data are a key component of the evidence supporting the effectiveness of this novel drug and are of interest to all stakeholders. Treatment persistence and adherence to tofacitinib are good overall and similar to those seen for bDMARDs.*

Introduction

Disease modification is the mainstay of rheumatoid arthritis (RA) treatment (1). Several efficacious disease-modifying anti-rheumatic drugs (DMARDs) are currently available, including conventional synthetic (cs) DMARDs, biologic (b) DMARDs and the recently developed class of targeted synthetic (ts) DMARDs (1). Currently, two tsDMARDs are available, tofacitinib and baricitinib, which are both inhibitors of Janus kinase (JAK).

Tofacitinib is a small-molecule, oral selective inhibitor of JAK1 and JAK3 and, to a lesser extent, of JAK2 (2). JAKs mediate signal-transduction activity initiated by the surface receptors for several cytokines, thus playing a key role in lymphocyte activation, proliferation and function (2). Tofacitinib (5 mg twice daily, oral administration) was approved in November 2012 by the US Food and Drug Administration (FDA) and in March 2017 by the European Medicines Agency (EMA) for treatment, with or without methotrexate (MTX), of moderate to severe active RA in adult patients who have responded inadequately to, or do not tolerate one or more DMARDs (3, 4). Tofacitinib has been included by the European League Against Rheumatism (EULAR) and by the American College of Rheumatology (ACR) among the treatments recommended for second- and later lines in RA (1, 5).

The efficacy and safety of tofacitinib, alone or combined with MTX, have been extensively evaluated in a series of phase II and phase III randomised controlled trials (RCTs) of 6–24 months duration (6-18), including the ORAL

programme, consisting of a series of large, phase III, randomised controlled trials (RCTs) in a variety of settings (6-13). Two global long-term extension studies, including 4967 RA patients who had completed prior phase I, II, or III studies of tofacitinib, have confirmed the sustained efficacy (>6 years) and consistent safety profile (>8 years) of tofacitinib administered as either monotherapy or in combination with csDMARDs (19).

RCTs have the most reliable study design to determine the efficacy and safety of drugs, and occupy a top position in the hierarchy of evidence supporting the approval of novel therapeutic agents (20-22). In such trials, a number of inclusion and exclusion criteria are used to select a clearly defined group of patients who are likely to benefit from the treatment under investigation. This can, however, compromise the external validity and reduce the generalisability of the study findings to real-world patients (20-22). Thus, the efficacy of a therapeutic intervention does not necessarily imply its ability to work under real-life conditions and to provide benefits that are important for patients, in other words, its effectiveness. The incomplete overlap of efficacy and effectiveness is described in the literature as the "efficacy-effectiveness gap" (21, 23). Regulatory authorities and decision-makers increasingly regard real-world evidence as a key component of the body of evidence supporting the effectiveness of a therapeutic intervention (20, 24-26). Observational studies evaluating the effects of treatment in routine clinical practice and outside of the highly controlled environment of RCTs are the main source of real-world data (24).

Extensive observational research on tofacitinib in RA is ongoing worldwide, and a significant body of real-world data from clinical practice is now becoming available. In this narrative review, we provide an overview of the real-world evidence for tofacitinib in RA as of March 2018. We will first discuss examples of the efficacy-effectiveness gap in RA and the importance of real-world evidence in bridging this gap, and in complementing the data from RCTs. We will then review the most relevant data on the use and effectiveness of tofacitinib in routine clinical practice.

Importance of real-world data in rheumatoid arthritis

Following the introduction of bDMARDs for RA, several national registries have been implemented to evaluate the long-term effectiveness and safety of these therapies. Registries have proven particularly valuable in RA (20, 27). For example, the current status of MTX as the gold standard first-line of disease-modifying interventions has emerged from long-term observational studies rather than from RCTs (25). In contrast with early RCTs, which failed to demonstrate the superiority of MTX over other csDMARDs, subsequent observational studies revealed that drug survival was markedly longer with MTX than with other csDMARDs (25). More recently, an observational study recognised the increased risk of opportunistic infections associated with inhibitors of tumour necrosis factor (TNFi), which did not emerge from the prior RCTs (28, 29). The effectiveness of tuberculosis prevention and screening before treatment with TNFi was also demonstrated by observational studies (25, 28).

With the purpose of investigating the efficacy-effectiveness gap in the evidence supporting current RA therapies, several studies have compared the characteristics of patients enrolled in RCTs and patients included in registries, which have found substantial differences between the two populations (30-33). Using data from the German biologics register Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT), it was investigated how many RA patients treated with a TNFi would have been eligible for the RCTs that led to the approval of the TNFi (33). The study found that only a minority of the patients (<35%) in the RABBIT register would have been eligible for the trials. In these patients, ACR20 and ACR50 response rates were comparable with those reported in published trials. In the register patients considered ineligible for the trials, ACR response rates were lower, although absolute improvements were similar to those in patients eligible for the trials, thus showing that ineligible patients nevertheless had some benefit from the treatment. Similar results were reported by the analysis of the Finnish National Register for Biologic Treatment including patients who started a TNFi between 2004 and 2014 (30). A recent study reviewed the eligibility criteria of 30 RCTs that included bDMARDs and tofacitinib and applied them to two observational cohorts of RA patients with more than 1500 patients each (32). This study, as well, found that only a minority of patients in both cohorts, ranging from 3.7% to 7.1%, satisfied the RCT inclusion criteria. Two systematic reviews of studies analysing the characteristics of RA patients participating in RCTs and observational studies of bDMARDs confirmed the existence of differences between the two groups (31). Compared with patients enrolled in RCTs, those from real-world observational studies had worse prognostic factors, including older age, longer disease duration, and >1 prior DMARDs. According to the authors, data from selected patient populations participating in RCTs may result in an overestimate of the effects in patients in real-world settings (31).

Overall, these findings have contributed to the general consensus among regulatory authorities, decision-makers and clinicians about the urgent need for more real-world observational studies, as RA patients participating in RCTs represent only a minority of those encountered in routine clinical practice.

Real-world treatment of rheumatoid arthritis with tofacitinib

Real-world evidence concerning tofacitinib in RA has just begun to emerge. The most substantial body of real-world evidence comes from clinical practice in the US, where tofacitinib has been available since 2012. Other countries contributing to the body of real-world evidence include Japan, Taiwan, Switzerland, Latin America and Russia. Source of real-world data are administrative claim databases, clinical databases, registries, including RA registries, and national pharmacovigilance programmes. Understanding treatment patterns and patient outcomes and

characterising the safety profile of tofacitinib are the principal objectives of real-world observations.

Patient characteristics, treatment patterns, and outcomes

Relevant real-world data are summarised in Table I. A study using US administrative claims data compared patient characteristics, treatment patterns and costs in RA patients receiving tofacitinib or common bDMARDs following one previous bDMARD, from 2012 to 2014 (34). Overall, 392 patients initiated tofacitinib, 178 adalimumab, 118 etanercept and 191 abatacept. Tofacitinib was more commonly used as monotherapy than bDMARDs; patients receiving tofacitinib monotherapy were more likely to remain on monotherapy during the 12-month follow-up. Persistence in treatment and adherence were comparable with tofacitinib and bDMARDs. Tofacitinib was associated with lower adjusted mean RA-related total costs *versus* adalimumab, etanercept and abatacept. Tofacitinib patients had a greater previous use of bDMARDs than the bDMARD cohort. A subsequent study using the same source of real-world data, conducted between 2014 and 2017 and focused on patients with no pre-index use of bDMARDs and tofacitinib, found that tofacitinib was more frequently prescribed as monotherapy than adalimumab or etanercept and confirmed the other main findings of the previous study (35).

The Corrona registry, founded in 2001, is one of the largest US-based RA observational registries (27). A study analysing the data from this registry investigated the use of TNFi and tofacitinib monotherapy or combination therapy with MTX by line of therapy in US clinical practice (36). The primary objective was to compare the prevalence and effectiveness of TNFi monotherapy *versus* TNFi combination therapy; the secondary objectives were to compare the prevalence and effectiveness of tofacitinib monotherapy *versus* tofacitinib combination therapy, as well as *versus* TNFi combination therapy. The study included patients initiating tofacitinib or TNFi and followed for 6 months. Among patients who initiated tofacitinib (n=555), 338 (61%) used it as monotherapy; the prevalence of monotherapy by line of therapy was 47%, 58% and 63% for second-, third- and fourth-line therapy, respectively. Among patients initiating a TNFi (n=7976), 2531 (31%) used monotherapy; the prevalence of monotherapy by line of therapy was, respectively, 21%, 36%, and 42%. In the matched populations, across outcome measures, TNFi combination therapy was more effective than TNFi monotherapy in second-line [rates of low disease activity (LDA), defined as Clinical Disease Activity Index (CDAI) ≤10 at 6 months, 55.6% *vs*. 47.1%], with differences diminishing in third- and fourth-line. Tofacitinib combination therapy with MTX was similar to monotherapy in the third- and fourth-line combined (LDA 35.2% *vs*. 31.1%). Tofacitinib monotherapy was similar to TNFi combination therapy in the third- and fourth-line combined (LDA 33.6% *vs*. 37.5%).

Another study based on the Corrona registry, which focused on safety, showed that patients initiating tofacitinib had longer disease duration than those initiating bDMARDs and csDMARDS (respectively, 13.4, 10.1 and 4.8 years); patients initiating tofacitinib had also been exposed to a higher mean number of previous TNFi (1.8) or bDMARDs (2.8) than patients initiating a bDMARD (mean number of previously used biologics: 1.1 TNFi and 1.4 non-TNFi bDMARDs) (37).

In a prospective, observational Japanese study, 113 patients who initiated treatment with tofacitinib alone or in combination with MTX were followed for 6 months (38). RA disease activity was evaluated based on the CDAI at several time points during the observation period. Within 6 months of tofacitinib treatment, 57.5% of patients achieved a CDAI50 response and maintained it for 6 months (responders); 42.5% had no CDAI50 response at 6 months (non-responders). Sixteen patients (14.2%) completed the 6-month treatment with tofacitinib without achieving a CDAI50 response, 17 patients (15.0%) dropped out for lack or loss of efficacy and 4 patients (3.5%) due to adverse events. Non-responders were more likely than responders to have advanced stage disease (68.8% *vs*. 38.5%, p=0.002) and to have received previous bDMARDs (85.4% *vs*. 55.4%, p=0.001). The number of previous bDMARDs used by non-responders was twice that used by responders (2.2 *vs*. 1.1, p<0.001). Concomitant MTX use was reported less frequent in non-responders than in responders (60.4% *vs*. 81.5%, p=0.019). Multivariate logistic regression analysis identified previous use of bDMARDs as a strong risk factor for the failure to achieve a CDAI50 response [odds ratio (OR) 4.48, 95% CI 1.73–11.63, p=0.002]. The study also compared baseline characteristics and therapeutic outcomes between biologic-experienced (n=77) and biologic-naïve (n=36) patients. Biologic-experienced patients were more likely than biologic-naïve patients to have advanced-stage RA (66.2% *vs*. 19.4%, p<0.001) and longer disease duration (12.8 years *vs*. 9.6 years, p=0.004). Tofacitinib was prescribed in combination with MTX less frequently in biologic-experienced than in biologic-naïve patients (59.7% *vs*. 100%, p<0.001). At 6 months, biologic-experienced patients had higher disease activity than biologic-naïve patients (mean CDAI scores, 11.4 *vs*. 4.8, p=0.001). Biologic-experienced patients were significantly less likely to achieve CDAI50 (46.8% *vs*. 80.6%, p=0.001), CDAI70 (31.2% *vs*. 69.4%, p<0.001) and CDAI85 (22.1% *vs*. 52.8%, p=0.002) responses than biologic-naïve patients; they had significantly lower remission rates (11.7% *vs*. 41.1%, p=0.001), higher drop-out rates (35.1% *vs*. 13.9%, p=0.025) and rates of drop-out due to lack or loss of efficacy (20.8% *vs*. 2.8%, p=0.011) than biologic-naïve patients.

Another 6-month observational study in Japan enrolled 70 consecutive RA patients who initiated tofacitinib at a rheumatology centre between 2013 and 2016 (39). Clinical disease activity was assessed using the DAS28-ESR score, simplified disease activity index (SDAI) and CDAI. Overall, 68.6% of patients used tofacitinib in combination with MTX, and the majority had previously used bDMARDs, while 31.4% were biologic-naïve. At 6 months, 82.9% of patients were still taking tofacitinib; 7 patients (10.0%) discontinued the drug

Table I. Patient characteristics, treatment patterns and outcomes in real-world studies with tofacitinib.

Study	Data source	n	Design and patients	Objectives	Tofacitinib treatment pattern	Main findings	Trt persistence and adherence
Harnett *et al*. 2016	US administrative claims database (2012-2014)	392, TOFA; 178, ADA; 118, ETN; 191, ABA	Retrospective cohort analysis of pts with 1 prior bDMARD initiating a bDMARD or TOFA	To compare characteristics, trt patterns, and costs of TOFA *vs*. bDMARDs over 12 mths pre- and post-index trt initiation	As monotherapy (53.1%) or in combination with csDMARDs (mostly MTX)	12-mth pre-index bDMARD use 77.6% in TOFA group *vs*. 47.6%-59.6% in bDMARD cohort. More pts on TOFA started and stayed on monotherapy *vs*. with bDMARDS. TOFA costs lower	Comparable persistence and adherence among cohorts
Smith *et al*. 2017	US administrative claims database (2014-2017)	184, TOFA; 1771, ADA; 1472, ETN	Retrospective cohort analysis of biologic-naïve pts initiating a bDMARD or TOFA	To compare characteristics, trt patterns, and costs in pts receiving TOFA *vs*. bDMARDs over 12 mths post-index trt initiation	TOFA used significantly more as monotherapy (34.2%), than ADA (21.7%) and ETN (26.5%)	Higher RA-related 12-mth pre-index costs and worse comorbidity score with TOFA. Monotherapy more frequent with TOFA. Total RA-related post-index costs lower with TOFA	Comparable persistence and adherence among cohorts
Reed *et al*. 2017	US Corrona Rheumatoid Arthritis registry (2001-2016)	555, TOFA; 7976, TNFi	Retrospective analysis Pts initiating a TNFi or TOFA, with 6-mth follow-up	Primary: To compare use and effectiveness of TNFi monotherapy *vs*. TNFi combination therapy Secondary: To compare use and effectiveness of TOFA monotherapy *vs*. TOFA + TNFi	Monotherapy rate with TOFA: 61% Monotherapy rate with TNFi: 31%	Higher LDA rates with TNFi combination therapy *vs*. monotherapy. Similar LDA rates for TOFA mono- *vs*. combination therapy and *vs*. TNFi combination therapy	NA
Kavanaugh *et al*. 2016	US Corrona Rheumatoid Arthritis registry (2012-2016)	760, TOFA; 4628, bDMARD; 1328, csDMARD	Interim analysis of a 5-yr. prospective observational study	To evaluate the safety of TOFA	NA	Disease duration at baseline longer in TOFA *vs*. bDMARD and csDMARD initiators. N. of prior bDMARDs and TNFi higher in TOFA *vs*. bDMARD initiators Safety data, see Table II	NA
Mori *et al*. 2017	Rheumatology centre in Japan (2013-2016)	113, TOFA (36 biologic-naïve, 77 biologic-experienced)	6-mth prospective observational study in pts initiating TOFA	To compare effectiveness of TOFA in biologic-naïve *vs*. biologic-experienced pts	As monotherapy or in combination with MTX Combination with MTX more frequent in biologic-naïve pts	57.5% CDAI50 response rate at 6 mths Significantly higher CDAI50 response and remission rates in biologic-naïve *vs*. biologic-experienced pts Prior bDMARD use strongly associated with non-response	15% drop-out rate for inefficacy 3.5% drop-out rate for AEs Higher drop-out rate in biologic-experienced *vs*. biologic-naïve pts

Study	Data source	n	Design and patients	Objectives	Tofacitinib treatment pattern	Main findings	Trt persistence and adherence
Iwamoto *et al*. 2017	Rheumatology centre in Japan (2013-2016)	70, TOFA	6-mth prospective observational study in pts initiating TOFA	To evaluate the effectiveness and safety of TOFA	Mostly in combination with MTX (68.6%) but also as monotherapy	Rapid significant decreases in disease activity and disability over 6 mths, also with monotherapy and after switching from TOCI Significant and inverse association of prior bDMARD use and LDA achievement Safety data, see Table II	82.9% trt persistence at 6 mths
Kyburz *et al*. 2016 and Finckh *et al*. 2018	Swiss Clinical Quality Management registry (2013-2016)	376, TOFA; 928, TNFi; 692, non-TNFi	Observational cohort study in pts initiating TOFA or bDMARDs	To characterize pts initiating TOFA and to identify factors determining the choice of TOFA or bDMARDs To compare drug retention rates with TOFA, TNFi, and non-TNFi bDMARDs	TOFA and non-TNFi used as monotherapy more often than TNFi TOFA preferentially given to pts with more prior bDMARDs, older age, and longer disease duration	TOFA initiated as 2nd-line in 25% of pts; after 1 *vs*. ≥2 bDMARD in 20% *vs*. 55% Pts with ≥2 prior bDMARDs, older age, higher BMI, or higher disability more likely to receive TOFA *vs*. TNFi More prior bDMARDs and higher BMI associated with increased discontinuation	Similar crude persistence among the 3 groups After adjustment for confounders, higher risk of discontinuation with TNFi *vs*. TOFA
Müller *et al*. 2017	St. Gallen Cohort, Switzerland (2013-2017)	58, TOFA	Prospective observational study in pts initiating TOFA 1.7 years mean follow-up	Primary: to analyse TOFA safety Secondary: to determine rate and time to LDA and remission	86% of pts initiated TOFA after ≥1 bDMARD	63.8% *vs*. 53.4% pts achieved LDA or remission after 62.0 *vs*. 65.3 days Safety data, see Table II	57% trt persistence Mean 112 days, to any-cause stop
Schneeberger *et al*. 2017	Rheumatology centres from 6 countries in Latin America	288, TOFA	Retrospective analysis in pts initiating TOFA	Evaluate the safety profile of TOFA	Monotherapy (41%) with csDMARD (59%) 2nd-line in 44%, after ≥1 *vs*. ≥2 bDMARDs in 18% *vs*. 38%	Safety data, see Table II	NA
Sansinanea *et al*. 2017	Medical records from rheumatology centres in Argentina (2014-2016)	62, TOFA	Retrospective analysis	Evaluate safety profile of TOFA	Mostly in combination with csDMARD (87%) As 2nd-line in ca. 60% After 1 *vs*. ≥ 2 bDMARDs in 19.3% *vs*. 21.0%	Safety data in Table II.	NA
Karateev *et al*. 2016	Russian REMARCA research programme	120, TOFA	Retrospective analysis	Evaluate effectiveness and safety of TOFA	Combination therapy with MTX (70%) or other csDMARD (10%); as monotherapy (20%)	Effective disease activity control during short-term follow-up (up to 6 mths)	NA

ABA: abatacept; ADA: adalimumab; AE: adverse event; bDMARD: biologic DMARD; BMI: body mass index; CDAI: clinical disease activity index; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying anti-rheumatic drug; ETN: etanercept; LDA: low disease activity; MTX: methotrexate; mth: month; N: number; RA: rheumatoid arthritis; TNFi: tumour necrosis factor inhibitor; TOCI: tocilizumab; TOFA: tofacitinib.

Table II. Summary of safety data from real-world studies with tofacitinib.

Study	Data source	Patients with RA (n)	Objective	Main findings	Discontinuation rate due to AEs
Cohen *et al*. 2018	Manufacturer's post-marketing surveillance safety database (2012-ongoing; 3-yr. interim data)	Pts worldwide initiating TOFA	Determine the post-marketing safety profile of TOFA	34,223 py post-marketing exposure 25,417 AEs reported; 4352 SAEs (17.1%); 102 fatal events (0.4%) Drug ineffective, 13.2%; headache, 9.0%; pain, 6.4%; fatigue, 6.0%; nausea, 6.0%; condition aggravated, 5.9%; diarrhoea, 5.8%; arthralgia, 5.2% RR/100 py of SAEs: 2.57, infections; 0.91, GI disorders; 0.60 respiratory disorders; 0.45, neoplasms; 0.43, cardiac disorders; 0.12, hepatobiliary disorders Stable RR of lymphoma with increasing exposure to TOFA	NA
Curtis *et al*. 2016	US health plans (2010-2014)	Pts initiating TOFA (2526), TNFi 42,850), ABA (12,305), RIT (5078), TOCI (6967)	Evaluate the risk of HZ and HSV infection associated with TOFA vs. bDMARDs	Crude IR of HZ for TOFA, 3.87/100 py, *vs*. 1.95-2.71/100 py for bDMARDs HR of HZ for TOFA vs. ABA: 2.01 (95% CI, 1.40-2.88)	NA
Kavanaugh *et al*. 2016	US Corrona Rheumatoid Arthritis registry (2012-2016; 3-yr. interim analysis)	Pts initiating TOFA (760), bDMARD (4628), or csDMARD (1328)	Evaluate the IR of AEs of interest in pts initiating TOFA, bDMARDs, or csDMARDs	Comparable IR of serious infection, CV events and malignancies among the three groups	NA
England *et al*. 2016	US National Data Bank for Rheumatic Diseases (1998-2015)	Pts (11,582) without prevalent cancer; 222, TOFA; 4419, TNFi; 1621, non-TNFi bDMARDs; 5320 csDMARDs	Evaluate the association between trt with bDMARDs or TOFA and incident cancer	1456 incident cancers (812 excluding NMSC) IR/1000 py of solid tumours 11.38 for TOFA and 3.40-7.50 for other trts IR/1000 py of lymphoproliferative disease, 0 for TOFA and 10.71-22.73 for other trts Estimates of RA trt-related cancer risk are still imprecise	NA
Machado *et al*. 2017	US MarketScan® Databases (2010-2014)	Pts previously treated with MTX (21,832) and prescribed csDMARDS (24.7%), TNFi (61.2%), non-TNFi bDMARDs (13.3%), or TOFA (0.8%)	Compare retrospectively incidence of serious infections among trt groups	IR/100 py of serious infection: TOFA, 3.7; other groups, 2.00-2.53; reference group (no treatment), 1.96 Adjusted HR for serious infection infection *vs*. reference group: TOFA, 1.81; csDMARDs, 0.82; TNFi, 1.13; non-TNFi bDMARDs, 1.10	NA
Mimori *et al*. 2017	Japanese post-marketing surveillance data (6-mth analysis)	Consecutive pts (2882) initiating TOFA	Evaluate the effectiveness of TOFA	1241 py post-marketing exposure; ≥1 AE in 33.5%; most frequent: infections (12.7%), HZ (3.3%), abnormal liver enzymes (1.7%). SAEs 7.7%, serious infection 3.5%, malignancies 0.4%, died 0.6%	9.6%

Study	Data source	Patients with RA (n)	Objective	Main findings	Discontinuation rate due to AEs
Iwamoto *et al*. 2017	Rheumatology centre in Japan (2013-2016)	Consecutive pts (70) initiating TOFA and followed-up for 6 mths	Evaluate efficacy and effectiveness of TOFA	20% reported ≥1 AE Infections (HZ) were the most common AE (15.7%)	5.7%
Mori *et al*. 2017	Rheumatology centre in Japan (2013-1016)	Pts initiating TOFA (113)	Compare effectiveness of TOFA in biologic-naïve vs. biologic-experienced pts	see Table I	3.5%
Chen *et al*. 2017	Medical centre in Taiwan (2015-2017)	Taiwanese pts (116) treated with TOFA (retrospective)	Evaluate the risk of HBV reactivation in pts treated with TOFA	Prior HBV infection in 81 pts (69.8%; 6 carriers, 75 with resolved infection). 4 of the 6 HBV carriers did not receive antiviral prophylaxis during TOFA trt 2 of the 4 carriers with no prophylaxis had HBV reactivation No HBV reactivation in other pts	NA
Müller *et al*. 2017	St. Gallen Cohort, Switzerland (2013-2017)	Consecutive pts (58) followed-up for a mean 1.7 yr	Evaluate the safety profile of TOFA	AEs leading to discontinuation: GI events (12), flare (3), pneumonia (2), blue toe syndrome (1), thoracic pain (1), myalgia (1) Moderate alterations in some laboratory tests: liver enzymes (12); decrease in Hb levels >10% (7); abnormal creatinine (1); lymphocyte count <1000/ml (4)	34.5%
Schneeberger *et al*. 2017	Rheumatology centres from 6 countries in Latin America	Pts (288) initiating TOFA and followed-up for a median of 22 mths	Evaluate the safety profile of TOFA	38 AEs reported Most frequent events: upper respiratory infections (11), skin infections (5), HZ (4), urinary tract infections (4)	3.8%
Malpica *et al*. 2017	Rheumatology centre in Colombia (2015-2016)	Pts (56) treated with TOFA for a mean of 33 weeks	Evaluate the safety profile of TOFA	17.9% with ≥1 AE; events mostly mild-moderate (1 severe event. Most reported AE: abdominal discomfort (3) Other reported AEs: diarrhoea (1), infection (1), mouth papules (1), rash (1), sinusitis (1), headache (1), folliculitis (1), pancreatitis (1)	NA
Sansinanea *et al*. 2017	Medical records from rheumatology centres in Argentina (2014-2016)	Pts treated with TOFA (62) and followed-up for up to 21 mths	Evaluate the safety profile of TOFA	6 AEs: HZ (2), upper airway infection (1), transient increase in liver enzyme (1), facial paralysis (1) tachycardia (1)	3.2%

ABA: abatacept; AE: adverse event; bDMARD: biologic DMARD; CI: confidence interval; csDMARD: conventional synthetic DMARD; CV: cardiovascular; DMARD: disease-modifying anti-rheumatic drug; GI: gastrointestinal; HBV: hepatitis B virus; HR: hazard ratio; HZ: herpes zoster; HSV: herpes simplex virus; IR: incidence rate; MTX: methotrexate; mth: month; NMSC: non-myeloma skin cancer; py: patient-year; RA: rheumatoid arthritis; RIT: rituximab; RR: reporting rate; TNFi: tumour necrosis factor inhibitor; TOCI: tocilizumab; TOFA: tofacitinib.

for lack of efficacy and 4 (5.7%) due to adverse events. Treatment with tofacitinib was associated with rapid and significant improvements in all disease activity scores from baseline to 6 months. Subgroup analysis by use or non-use of concomitant MTX showed that tofacitinib was associated with significant improvements in disease activity scores regardless of whether used in combination with MTX or as monotherapy. The study also analysed the effectiveness of tofacitinib in patients who failed treatment with the interleukin (IL)-6 inhibitor tocilizumab. These patients also experienced significant improvements in disease activity scores from baseline to 6 months, even though less substantial than those reported by the overall population; 25% achieved disease remission at 6 months. Of several baseline variables tested in a multivariate regression model, only the number of previously used bDMARDs was significantly and independently associated with achievement of LDA at 6 months.

The effectiveness of tofacitinib has also emerged from other small observational studies, which have confirmed that in clinical practice tofacitinib is used both in combination with MTX and as monotherapy, and is usually reserved for second- and later lines of treatment, as currently recommended (Table I) (40-45). Notably, analysis of the Swiss Clinical Quality Management registry including almost 2000 patients initiating treatment with tofacitinib, TNFi, or non-TNFi bDMARDs between 2013 and 2016 found similar crude drug retention rates for the three cohorts (40-45). After adjustment for potential confounders, a higher risk of discontinuation was associated with TNFi *versus* tofacitinib [hazard ratio (HR) 1.27, 95% CI 1.02–1.57, p=0.03], but not with non-TNFi *versus* tofacitinib (HR 1.03, 95% CI 0.83–1.28, p=0.76). A higher number of prior bDMARDs and greater BMI values were also significantly associated with an increased risk of discontinuation.

Safety profile

Relevant safety information from real-world data is summarised in Table II. In 2012, the manufacturer of tofacitinib instituted a safety database for worldwide post-marketing surveillance of the drug. Interim analysis of the data entered in the safety database from November 2012 to November 2015 was recently published (46). Most data (99.1%) were from post-marketing reports spontaneously submitted to the drug manufacturer by healthcare professionals or patients. Most originated in the US (73.9%). Overall, the worldwide exposure to tofacitinib during the 3-year reporting period was estimated to be 34,223 patient-years. In total, 25,417 adverse events, 4352 (17.1%) severe adverse events and 102 (0.4%) fatal cases were reported. Adverse events with a frequency ≥5% were: ineffective drug (13.2%), headache (9.0%), pain (6.4%), fatigue (6.0%), nausea (6.0%), condition aggravated (5.9%), diarrhoea (5.8%) and arthralgia (5.2%). The estimated incidence rates of severe adverse events per 100 patient-years were: 2.57 for infections, 0.91 for gastrointestinal disorders, 0.60 for respiratory disorders, 0.45 for neoplasms, 0.43 for cardiac disorders and 0.12 for hepatobiliary disorders. Non-melanoma skin cancer was the most frequently reported malignancy during the 3-year post-marketing surveillance programme of tofacitinib, with 16 serious cases reported. There were 15 cases of lymphoma, with no increase in reporting frequency with increased exposure to tofacitinib. No new safety issues were reported compared with the safety profile of tofacitinib seen in the RA clinical development programme.

Based on US health plan data, a study evaluated the risks of herpes zoster (HZ) and herpes simplex virus (HSV) infection among RA patients with no history of HZ or HSV infection, initiating tofacitinib or bDMARDs (47). A total of 2526 patients initiating tofacitinib were compared with patients initiating TNFi (n=42,850), abatacept (n=12,305), rituximab (n=5078) and tocilizumab (n=6967). The estimated crude incidence of HZ associated with tofacitinib was 3.87/100 patient-years and was in agreement with that seen in the tofacitinib clinical trial programme (3.3/100 patient-years) (47). After multivariate adjustment, HZ risk was found to be significantly more elevated with tofacitinib compared with abatacept, which was taken as reference given its common use as a second- or subsequent-line therapy in RA (HR 2.01, 95% CI 1.40–2.88). Tofacitinib was also associated with the greatest incidence of the combined outcome (7.61/100 patient-years, HR 1.40, 95% CI 1.09–1.81). Rates and adjusted HRs for all other bDMARDs were comparable to each other and abatacept. Of note, older age, female sex, prednisone >7.5 mg/day, prior infection and greater number of hospitalisations were associated with increased HZ risk, whereas vaccination was associated with a lower risk.

A 5-year study based on the US Corrona registry and evaluating the standardised incidence rates of adverse events of interest in three populations – tofacitinib initiators, bDMARD initiators, csDMARD initiators – is ongoing real-world (37). According to an interim analysis including 760 tofacitinib, 4628 bDMARD, and 1328 csDMARD initiators, the reported incidence rates of serious infections, cardiovascular events and malignancies in the three groups were similar despite differences in baseline characteristics (37). In tofacitinib, bDMARD and csDMARD initiators the respective incidence rates per 100 patient-years were 3.69, 3.29 and 2.39 for severe infections, 1.43, 0.94 and 0.47 for HZ, 1.81, 1.77 and 1.81 for malignancies, and 1.69, 2.57 and 2.59 for cardiovascular disease. Of note, the incidence rate of HZ in tofacitinib initiators (1.43/100 patient-years) was substantially lower than that reported by other real-world studies (47) and in the RCTs with tofacitinib (7).

A longitudinal observational study that included RA patients without prevalent cancer participating in the US National Data Bank for Rheumatic Diseases examined the association of bDMARDs and tsDMARDs with incident cancer in RA patients (48). Among 11,582 patients, 6262 biologic/tofacitinib and 5320 csDMARD initiators were identified; overall, 1456 incident cancers occurred during the observation period (1998–2015). Increased rates of solid tumours were found with tofacitinib; non-TNFi biologics were associated with increased rates of lymphoprolif-

erative malignancies. After adjustment for confounding variables, no increased risk of cancer with bDMARDs or tofacitinib was found relative to MTX monotherapy. Overall, the results were inconclusive and highlighted the difficulty of determining treatment-related cancer risk. Regarding non-melanoma skin cancer, which was the most frequently reported malignancy identified during post-marketing surveillance (46), an analysis of data from 18 studies in the tofacitinib RA clinical programme identified 83 cases among 6,092 tofacitinib-treated patients (15,103 patient-years) (49). There was no clear dose relationship, and the incidence rate was consistent with those observed in patients with RA treated with TNFi and other bDMARDS.

A retrospective analysis of real-world data from the US MarketScan® databases compared the incidence of serious infections associated with various treatments including tofacitinib in RA patients previously treated with MTX (50). The analysis included 21,832 patients: 0.8% treated with tofacitinib, 24.7% with csDMARDs, 61.2% with TNFi and 13.3% with other bDMARDs. The incidence of serious infections per 100 patient-years with tofacitinib was 3.7; in the other treatment groups, it ranged from 2.00 to 2.53 and was 1.96 for the reference group of patients with no prescribed treatment. The adjusted HRs for infections requiring hospitalisation were 1.81 (95% CI 1.08–3.01) for tofacitinib, 0.82 (95% CI 0.62–1.07) for csDMARDs, 1.13 (95% CI 0.92–1.38) for TNFi and 1.10 (95% CI 0.87–1.38) for non-TNFi bDMARDs *versus* the reference group.

The initial 6-month interim data from the ongoing post-marketing surveillance programme of tofacitinib in Japan have not yet revealed any new or unexpected safety issues compared with the adverse event profile reported in the registration RCTs (51). Overall, 2882 patients were enrolled, with an estimated exposure to tofacitinib of 1241.4 patient-years. Of these patients, 686 (23.8%) discontinued treatment. Discontinuations were due to adverse events in 276 cases (9.6%) and to lack of efficacy in 260 cases (9.0%). About one-third of the patients experienced at least one adverse event. Infections were reported by 367 patients (12.7%). The most frequent adverse events were HZ (3.4%) and abnormality in liver enzymes (1.7%). Severe adverse events occurred in 221 patients (7.7%). The most frequent severe adverse events were pneumonia (0.7%), interstitial lung disease (0.5%) and worsening of condition (0.4%). Infections were severe in 101 patients (3.5%). Malignancies were reported in 21 patients (0.7%). There were 16 deaths (0.6%) over the 6-month observation period.

A safety profile in line with the findings from RCTs has also been described in a number of other real-life observational studies as summarised in Table II (42-44, 52, 53). Of note, a recent retrospective analysis in a real-life cohort of 116 Taiwanese patients RA treated with tofacitinib evaluated the risk of hepatitis B virus (HBV) reactivation (52). Overall, 81 (69.8%) patients had a past HBV infection; 6 were defined as HBV carriers, while in 75 HBV infection was considered resolved. Among the 6 carriers, only 2 received antiviral prophylaxis during treatment with tofacitinib. Of the 4 carriers without antiviral prophylaxis, 2 experienced HBV reactivation during treatment with tofacitinib. No HBV reactivation was observed in patients with resolved infection.

Discussion and conclusions

The present narrative review provides, for the first time to the best of our knowledge, a summary of the real-world evidence concerning tofacitinib in the management of patients with RA. Despite the heterogeneity of the available sources of real-world evidence, a number of findings are consistent across the studies reviewed. With regards to patient characteristics, treatment patterns and outcomes, in the real-world setting patients initiating tofacitinib usually have longer disease duration and have been exposed to longer bDMARDs than patients initiating a bDMARD. Tofacitinib appears to be more frequently used as monotherapy than bDMARDs and to be effective without background MTX, in agreement with the results from the ORAL RCT programme (8). The real-world data also show that persistence in treatment with tofacitinib and adherence to treatment are good overall and similar to those seen for bDMARDs.

Two real-world studies have addressed the impact of prior bDMARD use on outcomes and shown that biologic-naïve patients initiating tofacitinib are more likely to achieve LDA or disease remission than biologic-experienced patients (38, 39). Furthermore, a significant and inverse association of the number of bDMARDs used with the achievement of LDA has been identified (38, 39). As a consequence, it may be advisable to introduce tofacitinib before failure of multiple bDMARDs. However, it is unclear at present which patients may benefit most from early introduction of tofacitinib, and further investigations are needed to clarify this point.

As for the safety profile of tofacitinib in real-world patients, with the exception of one study in which about one-third of patients interrupted treatment with tofacitinib due to adverse events (42), discontinuation rates for safety issues appear to be <10% (38, 39, 43, 44, 51). Overall, no unexpected safety events have been reported in the real-world setting and incidence rates of adverse events of interest (HZ, serious infections, opportunistic infections, malignancies, cardiovascular disease) appear to be similar to those reported in the RCTs (7, 19, 47).

In conclusion, this review provides a first glimpse into the real-world use and effectiveness of tofacitinib. Though essential for establishing the effectiveness of a treatment, data from post-marketing surveillance programmes are not without limitations: most reports are spontaneous, and the magnitude of non-reported cases is unknown (46). In addition, relevant clinical information is often missing or incomplete so that confounding effects that may contribute to reported adverse events cannot be identified (46). Clearly, more extensive and long-term data are needed to fully characterise the safety profile of tofacitinib, the optimal timing of treatment initiation and position of

JAK inhibition among the various targeted strategies available for treatment of RA.

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