Review

DOI: 10.5582/ddt.2022.01028

Real-world evidence of tofacitinib in rheumatoid arthritis patients in Spain

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SUMMARY The purpose of this narrative review is to provide an overview of the real-world data on the use of tofacitinib in patients with active rheumatoid arthritis (RA) in Spain. Sixteen retrospective studies carried out in Spain between 2019 and 2021 have been analyzed, considering patients' characteristics, and treatment patterns, effectiveness, and safety. In those studies, approximately 511 patients received tofacitinib during the study period. They were predominantly women (mean age: 48-61 years). The percentage of patients receiving tofacitinib as monotherapy ranged between 20.0% and 67.9%. Only five studies reported the combined use of corticosteroids (42.0-84.5% of patients), with a mean dose varying from 1.8 to 7.2 mg. A wide range of patients (36.0-85.7%) had failed a previous biological disease-modifying anti-rheumatic drug. The most frequent reason for treatment discontinuation was the lack of efficacy, and the most common adverse event described was herpes zoster infection. Real-world studies complement clinical trials by adding efficacy and safety data in real-world settings to the benefit/risk profile of the drug. The profile of RA patients receiving tofacitinib in Spain has similarities with other real-world studies conducted in other countries.

Keywords Tofacitinib, real-world data, rheumatoid arthritis, DMARD, JAK inhibitor

1. Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease characterized by persistent inflammation of the joints (*1*). Its worldwide prevalence is approximately 1%, and there is a higher incidence in women (*2*). In the case of Spain, the prevalence is 0.9% (*3*). Therapeutic resources for RA have increased considerably in the last 30 years and are used to control the devastating effects of its progression which include the destruction of the joints, the reduction in life expectancy, early unemployment, disability and cardiovascular (CV) damage (*4*). Among current pharmacological approaches for the treatment of RA are nonsteroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying anti-rheumatic drugs (DMARDs), with the latter dividing into conventional synthetic DMARDs (csDMARDs) such as methotrexate (MTX); biological DMARDs (bDMARDs) such as tumor necrosis factor (TNF) inhibitors; or targeted synthetic DMARDs (tsDMARDs) such as Janus kinase (JAK) inhibitors (*5*). The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) recommend csDMARDs, usually MTX, as the first-line therapy in patients with RA. However, sometimes it is not sufficient, and therefore patients with csDMARD inadequate response are recommended bDMARDs or tsDMARDs either alone or in combination with other csDMARDs (*6,7*). Tofacitinib is an orally bioavailable small molecule that inhibits by blocking the adenosine triphosphate (ATP) binding site. In human cells, tofacitinib preferentially inhibits signaling by heterodimeric cytokine receptors associated with JAK3 and/or JAK1 with functional selectivity over cytokine receptors that signal *via* pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib attenuates signaling of interleukins (IL-2, -4, -6, -7, -9, -15, -21) and type I and type II interferons, which results in modulation of the immune and inflammatory response (*8,9*). As specified in the European Medicines Agency (EMA) summary of product characteristics (SmPC), it is indicated for moderate to severe active RA in adult patients who have not responded adequately or are intolerant to DMARDs (*9*). It can be administered in combination with MTX or as a monotherapy (in case of intolerance or when treatment with MTX is not adequate). The recommended dose is 5 mg twice a day.

Tofacitinib was approved by the US Food and Drug

Administration (FDA) in November 2012 and by the EMA in March 2017 for the treatment of RA (*9,10*). The efficacy and safety of tofacitinib for the treatment of active RA in adults has been studied through numerous phase II, III, IIIb/IV and IV randomized clinical trials (RCTs) (*9*). Additionally, two long-term open-label trials have been completed (*11-23*). The results show sustained efficacy and consistent safety beyond 9.5 years (*24,25*). In a large (n = 4,362) randomized post authorization safety study (ORAL Surveillance [A3921133; NCT02092467]) in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of major adverse cardiovascular events (MACE) and malignancies was observed with tofacitinib compared to TNF inhibitors (*9*).

RCTs have been considered the *gold standard* for generating data on efficacy and safety, occupying a high position in the hierarchy of evidence that supports the registration of the product and its commercialization. However, these studies include patients with very selective profiles, and this strong internal bias may limit their external validity and, therefore, the transferability and generalizability of the results (*26,27*). Observational studies based on real-world data cannot replace RCTs to generate safety and efficacy data. However, they can help produce evidence of therapeutic effectiveness and support the RCT data, allowing comparisons in a real clinical setting (*28*). Therefore, supplementing data from clinical trials with real-world studies provides valuable information for payers, clinicians, and patients on how an intervention performs outside the narrow confines of the research environment. The importance of real-world evidence, to support marketed products and its potential role in product development/lifecycle monitoring and decision-making for regulation and evaluation, has been recognized by FDA (*29*) and EMA (*30*). Real-world data sources are administrative claims databases, clinical databases, RA patient registries, and national pharmacovigilance programs. Real-world evidence on tofacitinib has been published in different countries, including United States (*31,32*), Canada (*33*), Switzerland (*34*), and Australia (*35*) in cohort registries, as well as data sourced from other registries and hospital cohorts (*36,37*).

The purpose of this narrative review is to provide an overview of the evidence on tofacitinib use and the administration patterns in patients with active RA in the Spanish clinical practice.

2. Methods

A review of the literature was performed on diverse databases (PubMed, GoogleSchoolar) using the following keywords: "tofacitinib", "Janus kinase inhibitors", "rheumatoid arthritis", "Spain", "real-life". The search included all studies, case-series, and abstracts published between January 2019 and October 2021, written in English or Spanish. The date of search was October 22nd, 2021. Studies not involving patients with RA, those not from Spanish hospitals, those whose data is derived from clinical trials, or those without a minimal description of patient characteristics were not incorporated into the review. Given the scarce available literature, abstracts from the XLV, XLVI and XLVII National Congress of the Spanish Society of Rheumatology (held in 2019, 2020 and 2021) and from the Annual European Congress of Rheumatology (EULAR, held in 2020 and 2021) were also examined. From the identified studies, an analysis was made of patient characteristics, treatment patterns, effectiveness, and safety. To avoid duplicates, any abstracts from the same center were carefully analyzed and only the most recent data were presented.

3. Available real-world studies with tofacitinib for rheumatoid arthritis in Spain

Between 2019 and 2021, 16 retrospective studies reported the tofacitinib experience in patients with RA on routine clinical practice in Spain (*38-53*). Data from case-series were obtained from medical records and databases of a hospital's Rheumatology Service (Supplementary Table S1, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=94*). Data from the Spanish registry of adverse events (AEs) of biological therapies in rheumatic diseases (BIOBADASER 3.0), including information on the administration of JAK inhibitors, was not included in the analysis (*54*). The most relevant data obtained are summarized in Table 1 (demographics and baseline disease characteristics, Online Table, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=95*) and Table 2 (effectiveness and safety data, Online Table, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=95*).

3.1. Demographic characteristics

The total number of RA patients assessed in these studies were 1,108. 511 were treated with tofacitinib. The number of RA patients included in each series that were treated with tofacitinib varied, ranging from 4/81 (4.9%) (*44*) and reaching 81/81 patients (100%) in series that only included RA patients with tofacitinib (*45*). The mean age of patients analyzed ranged between 43.7 years (standard deviation, SD: 12.2 years) (*53*) and 61.2 years (SD: 13.2 years) (*43*), while the median age varied from 61.0 years (range: 40.0-74.0) (*41*) to 62.9 years (range: 49.9-74.4 years) (*46*). According to RA prevalence, a higher percentage of women received tofacitinib (between 58.0% [16/28 of patients] (*38*) and 94.4% [17/18]) (*41*). Only two studies described the comorbidities in 40 RA patients. In one study, 30.0% (12/40) had arterial hypertension, 32.5% (13/40)

dyslipidemia, 15% (6/40) diabetes mellitus, 10% (4/40) hypothyroidism, 32.5 % (13/40) smokers, and 20.0% (8/40) osteoporosis (*39*). In the other study, arterial hypertension (30.3% of patients, 20/66), diabetes mellitus (6/66, 9.1%), and dyslipidemia (26/66, 39.4%) were reported (*49*). The body mass index has been reported only in one study (*38*), where the mean value was 30.1 kg/m2 in 28 patients (19 of them had received tofacitinib). Also, only one study reported extra-articular manifestations, in 28.6% of patients (8/28) (*43*), 14 of whom had received tofacitinib.

3.2. Baseline disease characteristics

Disease duration of RA ranged from 8.7 years (SD: 6.5 years) (*49*) to 18.0 years (interquartile range: 9.0-22.0) (*50*). The percentage of patients who had failed with a previous bDMARD and received JAK inhibitors was reported to range from 36.0% (*48*) to 85.7% (24/28) (*43*). The mean treatment time with a bDMARD was between 2.6 years (SD: 3.0 years, in one study) (*44*) and 3.9 years (range: 1.2-10.9 years, in another study) (*40*). Including case-series, patients who did not achieve a therapeutic response to least one bDMARD varied from 15.4% (6/39) (*47*) to 41.4% (24/58) (*47*) of patients receiving JAK inhibitors. Those who had failed at least two previous bDMARDs ranged between 13.6% (9/66) (*49*) and 46.1% (18/39) (*46*), and those who had failed three or more previous bDMARDs ranged from 10.6% (7/66) (*49*) to 43.3% (39/90) (*45*). The use of JAK inhibitors in patients who had not received biologics previously was reported between 10.0% (9/90) (*45*) and 35.7% (10/28) (*38*). Two studies provide data about the reasons for switching to biologics. In the first study, the switching group included 35 patients (18 received JAK inhibitors) (*40*). The reasons for changing therapy were ineffectiveness (28/35, 80.0%), AEs (6/28; 17.1%), lack of follow-up (1/28, 2.9%). The mean duration on biologic therapy before switching was 3.9 years (range: 1.2-10.9 years). In the second study, the mean time in treatment with a bDMARD was 2.6 years (SD: 3.0 years) (*44*). The reasons to switch therapy in 81/252 patients were: loss of efficacy (25/81, 30.9%); AEs (31/81, 38.3%); change of address/loss of follow-up (20/81, 24.7%); and voluntary abandonment of treatment by the patient (5/81, 6.2%). One case-series provided data on sequential and switch treatment with JAK inhibitors, in any order, and evaluated the efficacy and safety of the second therapy when the first one had failed (*43*). This study included 28 patients, half of them received either tofacitinib or baricitinib.

Regarding autoantibodies status, the presence of rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (CCP) was reported in 69% (40/58) (*47*) and 72% (13/18) (*41*) of the cases. Only this latter study reported the frequencies of RF+/CCP- (1/18, 5.6%), RF-/CCP- (3/18, 16.7%), and RF-/CCP+ (1/18, 5.6%). One study reported CCP+ (19/28, 67.9%) (*43*), and another study reported RF+ (55/81, 68.0%) and CCP+ (61/81, 74.0%) (*44*) for any JAK inhibitors. Three studies reported these values separately: RF+ (32/39, 82.1%)/CCP+ (28/39, 71.2%) (*46*), and RF+ (9/9, 100.0%) / CCP+ (7/9, 77.8%) (*42*), and RF+ (87.5%, 35/40) / CCP+ (30/40, 75.0%) (*39*), in patients treated with tofacitinib. Structural damage data was included in six studies, describing erosive disease in 46.4% (13/28) (*43*), 54.5% (*51*), 62.5% (25/40) (*39*), 66.7% (6/35) (*42*), 67.8% (38/56) (*53*), and 87.2% (34/39) (*46*) of the patients treated with JAK inhibitors.

Disease activity at baseline was evaluated in nine studies with the Disease Activity Score 28 (DAS28), showing that patients who received JAK inhibitors had initially a moderate disease activity (defined as DAS28 score range: 3.2-5.1; DAS28: 4.3 (*48*), DAS28: 4.5, SD: 1.5 (*40*), DAS28/ C-reactive protein [CPR]: 4.5, range: 1.6-6.4, DAS28: 4.8, SD: 0.9 (*47*), DAS28: 4.8 (*38*), DAS28: 4.9, SD: 0.9 (*39*), and DAS28: 4.9, SD: 1.1 (*51*)); or high disease activity (DAS28: 5.2, range: 4.3-6.3; DAS28 score > 5.1, DAS28-CPR: 5.4, SD: 0.91 (*43*), DAS28-erythrocyte sedimentation rate [ESR]: 6.1, range: 3.8-5.3 (*42*)).

3.3. Tofacitinib administration patterns

The JAK inhibitors were administered either as monotherapy or in combination with csDMARDs or corticosteroids. The percentage of patients in each study where JAK inhibitors, specifically tofacitinib, were administered as monotherapy was 20.0% (8/40) (*39*), 24.8% (23/66) (*49*), 39.2% (*48*), 51.1% (46/90) (*45*), 59% (33/56) (*50*), 66.7% (12/18) (*41*), and 67.9% (19/28) (*38*). Related to combination therapy, the csDMARD which was most frequently used in combination with JAK inhibitors was MTX, ranging between 33.3% (6/18) (*41*) and 87.5% (35/40) (*39*), followed by leflunomide by up to 19% of patients (11/58), hydroxychloroquine by up to 13.8% (8/58) and sulfasalazine by up to 12.1% (7/58) (*47*). Only four case-series reported data regarding the combination of JAK inhibitors with corticosteroids, where 42.2% (46/109) (*40*), 72.5% (*52*), 73.9 (51/69) (*51*), and 84.5% (49/58) (*47*) of patients received corticosteroids. Mean administrated doses were reported in two studies, ranging from 1.8 mg (SD: 3.2 mg) (*46*) to 7.2 mg (SD: 4.2 mg) (*43*).

3.4. Effectiveness

The most relevant data regarding effectiveness and safety of tofacitinib are presented in Table 2 (Online Table, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=95*). Clinical response to JAK inhibitor therapy was assessed by determining an improvement on the DAS28 score, tender and swollen

joint counts, C-reactive protein, and erythrocyte sedimentation rate (ESR, from baseline), as well as the reporting rate of patients who achieved DAS28 remission and low disease activity (LDA). In a study with 40 patients treated with tofacitinib, the mean baseline DAS28 was 4.9 (SD: 0.94). This was reduced at 3 months to 3.1 (SD: 1.0) and remained at the same value at 6 months, *i.e*. 3.1 (SD: 1.1) (*39*). Similarly, another study reported a baseline median DAS28 of 6.1 (range: 3.8-5.3) and a final median DAS28 of 5.5 (range: 2.6-3.6) in a sample of 9 patients (*42*). Only one study reported a higher reduction in the DAS28, with a baseline median of 4.8 (range: 3.3-6.2) and a final median DAS28 of 2.61 (range: 2.5-3.7) (*46*).

The rate of RA patients in remission and the percentage of LDA were reported in three studies. In the first study (n = 40 patients) remission at month 3 was achieved in 27.5% of subjects (11/40), and LDA in up to 22.5% (9/40). At 6 months, 47.4% of patients (9/19) achieved remission and LDA in up to 42.1% (8/19) (*39*). The second study with 18 patients when it began, showed remission at 3 months as 76.9% (10/13), and LDA of up to 15.4% (2/13). At 6 months, there was a remission in all patients who continued treatment 100% (3/3) (*41*). The third study, with an initial number of 9 patients, reported a remission of 33.3% (3/9) and a LDA of up to 11.1% (1/9) (*42*).

Efficacy data for switching between JAK inhibitors (tofacitinib and baricitinib) were reported in a case series involving 28 patients (*43*). At the beginning of the study, 14 patients received tofacitinib and another 14 patients received baricitinib. After switching (both groups of patients: from tofacitinib to baricitinib, and from baricitinib to tofacitinib), the overall mean DAS28-CPR decreased at each visit: at 3 months 3.3 (SD: 1.0), at 6 months 3.2 (SD: 1.2) and finally, with 21 patients (75.0%) followed up to 12 months (mean: 2.2, SD: 0.6).

Persistence of treatment was reported in three studies, with a treatment time of 7.6 months (mean) (*43*), 8.9 months (SD: 5.1 months) (*47*), 13.2 months (median) (*46*), respectively. One study also compared the persistence between patients receiving tofacitinib in monotherapy (9/23, 39.1%) versus in combination with csDMARD (26/43, 60.5%) (*49*). One of the studies reported the survival rate for biologically experienced patients (81.7% and 78.7% at 6 and 12 months), and the pooled survival rate for JAK inhibitors (85.0% and 82.5% at 6 and 12 months). None of the JAK inhibitor treatments in patients with no biological experience were interrupted during the follow-up (18.4%, n = 18) (*38*). Another study reported survival rates of 85.0% and 70.0% at 6 and 12 months, respectively, when tofacitinib was used as first- or second-line treatment (*45*). Another study revealed a median survival of 35 months for patients receiving tofacitinib (*50*). Regarding the percentages of follow-up, one study showed 66.6% (6/9) (*46*) of patients remaining on treatment with tofacitinib, and another study showed 64.4% (29/45) (*47*).

In the study where treatment switching was done between JAK inhibitors, the mean survival for the first JAK inhibitor was 7.6 months (SD: 6.1 months). The mean follow-up after starting the second JAK inhibitor was 9.6 months (SD: 5.6 months). Survival in the second JAK inhibitor was 82% at 3 months, 76% at 6 months, and 62% at 12 months (*43*).

3.5. Safety

The objective of this review was not to evaluate safety because the number of patients included in these studies was too low for this purpose. Nonetheless, a brief review on the safety data related to JAK inhibitors were presented. Related to the occurrence of AEs, studies reported the percentage of AEs as between 15.0% (6/40) (*39*) and 39.0% (11/28) (*43*). The most frequent AEs in each study included: infections (68/122, 55.7%) (*53*), hypercholesterolemia (5/9, 55.5%) (*46*), and herpes zoster (HZ), with the latter being the most repeated AE throughout the studies, representing between 3.3% (4/122) (*53*) and 30.8% (4/13) of cases (*47*). Infections reported in several of the studies were respiratory infections 33.3% (2/6), odontogenic infections 16.7% (1/6) (*39*) and infections in general 69.7% (46/66). The rate of treatment discontinuation ranged between 12.5% (19/149) (*38*) and 33.9% (19/56) (*50*). The most frequent reasons for discontinuation were ineffectiveness (between 8.1% of patients, 5/62 (*48*) and 61.0%, 17/28 (*43*)) and AEs (from 2.6%, 4/149 (*38*), to 50.0%, 16/32 (*45*)). Infections and intolerance to treatment were only reported in one study, which occurred in 12.0% (2/16) and 22.0% (4/16) of patients respectively (*45*). Other less frequent reasons were the failure of the first treatment (between 3.0%, 2/66, and 5.3%, 1/19) (*38*), failure of the second treatment (21.1%, 4/19) (*38*), HZ (in 3/16 of patients, 16.0%) (*45*), refractory (2/3, 66.6%) (*46*), mayor embolic risk factors (10%) (*52*), and AEs (1/3, 33.3%) (*46*).

4. Integration of the real-world evidence

This review of real-world data in RA patients treated with tofacitinib is the first that has been conducted in a Spanish population. Information on clinical practice may also be influenced by geographic location as not only may the patients managed be of differing ethnic groups, but also the health systems will differ. Therefore, it is relevant to provide the results in Spain as well as contextualize them with other studies based on clinical experiences in real-world conditions. The world's most extensive data set of patients with these characteristics used for real-world studies have been primarily the Corrona registry in the United States,

with 1,544 patients (*31*), and the eXel program in Canada, with 1,226 patients (*33*). Others, such as the Australian study by Bird *et al*. (*35*) based on the OPAL dataset (Optimizing Patient outcomes in Australian RheumatoLogy), or the Swiss study by Finckh *et al*. (*34*) based on the registry SCQM-RA (Swiss Clinical Quality Management in Rheumatoid Arthritis), have reported 650 and 806 patients, respectively. In our present review, 13 retrospective case cohorts were collected from different Spanish hospitals, involving 386 patients treated with tofacitinib. The BIOBADASER 3.0 (*54*) study reported data from 669 patients treated with JAK inhibitors, but without individualizing the differentiating characteristics for JAK inhibitors. It reported comorbidities in patients such as current smokers (20%), diabetes (10%), ischemic heart disease (3%), hypertension (30%), heart failure (2%), interstitial lung disease (ILD, 2%), chronic obstructive pulmonary disease (COPD, 3%), chronic kidney disease (3%) and osteoporosis (16%) in patients treated with JAK inhibitors. Other studies reported data, such as that of Reed *et al*. (*32*) based on the registry of Corrona (402 patients, 238 in monotherapy and 164 in combination treatment), and Mueller *et al*. (*36*), based on the records of the hospitals of St. Gallen and Aarau in Switzerland. In general, all the studies showed a higher percentage of women, and the mean age of the patients was very similar, between 48 and 61 years (*43,44*). Nevertheless, compared to the Australian study by Bird *et al*. (*35*), with ages ranging between 55 and 74, Spanish RA patients treated with tofacitinib are younger in that series (median age ranges 61-62,9 and ages range 40-74.4), and in the BIOBADASER 3.0 the mean age of patients treated with JAK inhibitors was 59.6 (12.3 SD) (*54*).

It is rare to find collected data regarding comorbidities in patients. However, the Swiss register (*34*) considered CV diseases and osteoporosis of particular interest. In our review, the Gómez-Lechón Quirós *et al*. (*39*) study reported on comorbidities, and in de la Morena *et al*. (*38*), the body mass index was reported, with a mean value of 30.1 kg/m^2, representing a weight above normal, which represents a significant risk factor for the development of CV diseases. However, the percentages did not exceed 50% in any of the previous studies mentioned. The BIOBADASER 3.0 reported a comorbidities prevalence in RA patients treated with JAK inhibitors, but without specifying the type of JAK or other characteristics such as treatment line or reasons for prior failure (*54*). From the clinical point of view, it is of interest to consider the comorbidity of the patients, especially the cardiovascular risk factors (CVRF). In the ORAL Surveillance study, comparing the combined tofacitinib doses with a TNF inhibitor in a cardiovascular risk-enriched population, risks of MACE and cancers were higher with tofacitinib and did not meet noninferiority criteria (*55*). Several adverse events were more common with tofacitinib. In a real-world data (RWD) multidatabase in USA, a population-based study about the safety of tofacitinib in routine care patients with RA (STAR-RA study) included 102,263 patients, of whom 12,852 (12.6%) initiated tofacitinib. In this study tofacitinib was not associated with an increased risk of cardiovascular outcomes when compared with TNF inhibitor, however, tofacitinib was associated with an increased risk of cardiovascular outcomes in patients with RA with cardiovascular risk factors (*56*).

In our data, tofacitinib was mainly used in patients with active RA after failure to bDMARD treatment (*45*). This was true despite patients with worse prognoses than those included in clinical trials, with long disease duration and often with previous treatment with two or more bDMARDs (*38,39*). Previous experience with patients treated with at least one bDMARD can be found in real-world studies carried out in Canada (*33*) and Switzerland (*34,36*). On the other hand, in line with other publications (*32,57*), the findings of our study coincide with the fact that patients who start tofacitinib tend to have a longer duration of the disease and have been exposed to more DMARDs than patients who start with bDMARDs. Similar to other real-world series (US Corrona registry, Canadian registry) (*32,33*), tofacitinib is administered as monotherapy in a considerable percentage of patients (between 20% to 67.9%). Concerning combined therapy, the most frequently used csDMARD was MTX (39,41), and in the case of corticosteroid application, the doses were low (*47*). In Spain, some retrospective studies have compared the efficacy and safety of JAK inhibitors under real-world conditions, obtaining similar results (*37,38,41*).

Regarding survival, the Canadian study observed long-term survival of two years in patients receiving tofacitinib. Persistence was 62.7% and 49.6% after 1 and 2 years of treatment, respectively (*33*). In the Spanish population, the study with the most extended follow-up of survival was from Soleto *et al*. (*45*) which showed promising results with tofacitinib at 12 months. The frequency of interruption of treatment due to ineffectiveness is noteworthy, which could be related to refractory patients' clinical profile in the studies and/or the small sample used (*47*). The most commonly reported AE in retrospective studies among the Spanish population was HZ infection (*45,58*), which is in line with results by Kremer *et al*. (*31*) in the US, where the 5-year incidence rate of AEs was evaluated. A pulmonary embolism was also detected in a 70-year-old hypertensive patient (*47,49*). Finally, it is necessary to highlight that the variability found among Spanish studies (regarding evaluated variables) represents that observed in current routine clinical practice in Spain. Its causality might derive from differential features of involved patients. The main objective of this review is to show the tofacitinib usage patterns in Spanish

real-world studies. For that reason, safety trials in special populations and larger real-life series already published provide more conclusive safety results than those reflected in the present analysis. After evidence obtained from the ORAL Surveillance study, the SmPC has been updated to include recommendations in patients over 65 years of age, patients who are current or past smokers, patients with other cardiovascular risk factors, and patients with other malignancy risk factors (*9*). Prospective registers of RA patients who receive treatment with biological therapies in Spain might provide more data, from a methodological point of view (including a comparator control group), for the clinical practice in Spain; however, to date there are no published data.

5. Conclusion

This analysis describes the pattern of tofacitinib use in Spain and complements the data obtained from clinical trials. Despite being a review of real-world studies and inherently limited by the retrospective nature of the observational study (*i.e*., providing only available data), and the heterogenicity due to the different and independent cohorts, the results observed reflect patterns of treatment use in real-world settings. RA patients treated in Spain are slightly younger than in other registries, have previously used biologics and often receive tofacitinib monotherapy. The small series of patients included and the lack of data regarding ethnicity or race are some limitations of the study. Also, the mean follow-up of patients treated with tofacitinib is shorter compared to other real-world studies and clinical trials' follow-up. Long-term real-world data and pharmacovigilance information will increase knowledge about safety. Nonetheless, the study aimed to describe the tofacitinib pattern of administration in Spain. Data published from medical records and databases in Spain were consistent with the known benefit/risk profile of the drug, and with the main reason for discontinuing the drug being ineffectiveness. The most common AE was infection. A disease activity response was obtained in patients previously treated with bDMARDs. Further real-world evidence, collecting data more homogeneously, and providing novel variables (patient and clinician satisfaction, for instance) are required to strengthen the body of evidence for tofacitinib use.

Acknowledgements

Authors would like to express their gratitude to Pablo Vivanco (PhD, Meisys) for helping in the elaboration of the manuscript, and M Valderrama as Pfizer employee for contribution to the manuscript.

Funding: Pfizer provided the financial support for writing the manuscript.

Conflict of Interest: Llevat N and Montoro M both work in Pfizer´s medical department. Román Ivorra JA declares no conflicts of interest.

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Received March 28, 2022; Revised April 21, 2022; Accepted April 23, 2022.

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Released online in J-STAGE as advance publication April 29, 2022.