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Effectiveness and baseline predictive factors for Tofacitinib response in rheumatoid arthritis in a real-world setting: A national multicenter study

Abstract

Background: Evidence of effectiveness and safety of tofacitinib (TOF) in the real-world setting in Latin America is currently limited and crucial to complement long-term extension data from randomized controlled trials.

Methods: Patients initiated on TOF between 2014 and 2020 with RA (ACR/EULAR, 2010 criteria) were analyzed. The primary end point at month 3 was remission measured by DAS28-ESR. Secondary end points included prognostic factors for remission at 3 months and of monotherapy at month 12.

Results: Overall, 134 RA patients were analyzed. Remission was achieved in 38.06% at month 3. In univariate analysis, persistent disease activity at 3 months was observed in those patients with longer duration of disease, structural radiological damage, higher baseline DAS28-ESR and greater frequency in previous use of bDMARD. In multivariate analysis, previous use of bDMARD was significantly associated with a decrease in the probability of remission at 3 months. At 12 months, TOF monotherapy group was elderly ($p = 0.009$) and had a trend for lower frequency of anti-CCP. Treatment persistence was 94.78% at 3 months, 82.84% at 6 months and 66.42% at 12 months.

Conclusions: Clinical remission at 3 months was negatively associated with prior bDMARD and poor prognostic factors. TOF monotherapy at 12 months was more common in elderly patients.

Keywords: tofacitinib, Janus kinase inhibitor, rheumatoid arthritis, real-world settings, daily clinical practice

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Vinicki JP,[1] Gomez R,[2] Maliandi MR,[3] Velasco Zamora JL,[4] Malvano YS,[5] Cusa MA,[6] Gamba MJ,[2] Got J,[7] Gut O,[8] Paris V,[9] Spinetto MA,[8] Mariasch NC,[8] Abalo AI,[10] Estevez AJ,[10]

[1]Unidad de Reumatología, Hospital de Quilmes, Argentina
[2]Servicio de Reumatología, Hospital Posadas, Argentina
[3]Unidad de Reumatología, Sanatorio Garay, Argentina
[4]Instituto de Investigaciones Clínicas, Quilmes, Argentina
[5]Sanatorio Modelo Adrogué, Argentina
[6]Medicina Reumatológica, Centro Médico Privado, Argentina
[7]Unidad de Reumatología, Instituto Médico HUMANITAS, Argentina
[8]Centro Médico Privado, Argentina
[9]Unidad de Reumatología, Hospital Escuela de Agudos Dr. Ramón Madariaga, Posadas, Argentina
[10]Unidad de Inmunoreumatología, Hospital El Cruce, Argentina

Correspondence: Juan P Vinicki, MD, Unidad de Reumatología, Hospital de Quilmes, Hospital address: 770, Allison Bell, Quilmes (1878), Buenos Aires, Argentina, Tel + 54 9 11 2767 0998; Email jpvinicki@hotmail.com

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Introduction

Tofacitinib (TOF), an oral Janus kinase inhibitor, was approved by the local Argentinean regulatory agency (ANMAT: Administración Nacional de Medicamentos, Alimentos y Tecnología Médica) in 2013 for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) and an inadequate response/intolerance to methotrexate (MTX). The approved TOF dose for RA is 5 mg twice daily (BID); an extended-release formulation, dosed at 11 mg once daily, for the same indication has also been approved.

Clinical efficacy and safety of TOF have been extrapolated mainly from patient populations with active RA in phase 2 and phase 3 randomized controlled trials (RCTs), and long-term extension studies.[1–11] RA patients from Latin America (LatAm) differ from patients from the rest of the world in terms of genetic and epidemiologic factors, and in prognosis and so they could potentially elicit different clinical responses to a given mode of action.[12] Across Phase 3 studies and long-term extension studies of TOF, subpopulations from LatAm have been reported to experience similar improvements in efficacy than in patients from the rest of the world.[13] Likewise, the safety profile of TOF has been similar between these two groups of patients.[14] However, there is still a scarcity of published information regarding TOF therapy in a real-world settings (RWS) regarding its safety and effectiveness.[15–18] In LatAm particularly, there are almost no data available.[19–21] We therefore decided to assess the effectiveness, safety and drug survival of TOF in RA patients from Argentina. Additionally, baseline predictive factors for TOF response were studied.

Materials and methods

Study design and oversight, enrollment criteria, definitions and outcome variables

A retrospective multicenter observational study of RA patients diagnosed according to the ACR/EULAR 2010 criteria[22] seen at the outpatient clinics at 10 public or private rheumatology units from Argentina between 2014 and 2020 who had at least a 3-month follow-up after starting TOF was performed. Data were obtained from patients' medical records and stored in a computerized database. The data obtained at initiation of TOF therapy were gender, age, associated comorbidities, time from disease diagnosis to TOF initiation, laboratory markers when available (antinuclear antibody [ANA], anti-Ro, rheumatoid factor [RF], and anti-citrullinated peptide antibody [anti-CCP]), radiological joint damage (assessed if erosion in hands and feet x-rays were present at the time of starting TOF according to the treating physician), disease activity score-28 (DAS28), concomitant use and the corresponding dose of MTX and prednisone (PDN) and TOF dose. Also, previous use of conventional synthetic disease-modifying antirheumatic drugs (csDMARD) such as methotrexate (MTX) or leflunomide (LEF), biological disease-modifying antirheumatic drugs (bDMARD) like TNF-inhibitor (infliximab, adalimumab, etanercept, golimumab, certolizumab pegol) or IL-6-inhibitor (tocilizumab) or selective co-stimulation modulator (abatacept) or anti-CD20 monoclonal antibody (rituximab) was recorded.

DAS28 erythrocyte sedimentation rate (ESR) [DAS28-ESR], concomitant use of MTX and PDN information were collected, when available, at 3, 6, and 12 months from the initiation of TOF. In addition, if the patient continued TOF therapy or not and the duration of therapy were also recorded. In case of discontinuation, the reason and the description of the adverse events (AEs), if any, were recorded. Any abnormal clinical finding temporally associated with the use of TOF is described according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. The primary end point at month 3 was remission from baseline in disease activity measured by DAS28-ESR. Secondary end points included prognostic factors for remission at 3 months and of monotherapy at month 12.

Statistical analysis

Results are expressed as median and interquartile range 25th–75th (IQR) or mean±standard deviation for numerical variables and percentage for categorical ones. Comparisons of two different time values were performed using Wilcoxon sign test for numerical variables and McNemar´s test for categorical variables. To compare two independent groups Wilcoxon ranksum test and Fisher test were used for numerical and categorical variables respectively.

To examine the probability of clinical remission over time, defined as DAS28-ESR <2.6, a Hierarchical Linear Regression model was used for dichotomous dependent variables (Raudenbush and Bryk, 2002). To model the behavior of the dependent variable, a bilinear (bi-spline) model was used with a cut-off point at 6 months. Therefore, two linear slopes were examined for the probability of remission, one from the start of TOF treatment until month 6 and another from month 6 to month 12. The independent variables evaluated were gender, age, disease duration at entry into the study from diagnosis, structural joint radiological damage, previous MTX and bDMARD use and baseline DAS28-ESR. In all cases a p value < 0.05 was considered indicative of statistical significance. STATA 14.1 (StataCorp, Texas, USA) was used for the statistical analysis. Multivariate analysis were performed using R software and its library packages (Lme4, Tidyverse and ggpubr).

Results

Patients

Overall, 134 RA patients were analyzed. Sample description is presented in Table 1. The median age of the patients was 63 years (IQR 55-70), the median duration of RA was 8.0 years (IQR 4-18), and 76.1% were female. At baseline, most patients were positive for RF (86.6%), anti-CCP (82.0%) and 73.1% had radiological joint damage. Severe disease activity (DAS28-ESR > 5.1) was present in 70% of the patients, almost all patients had taken MTX or LEF before and 60% had not received prior bDMARDs. Patients with DAS28-ESR < 5.1 started treatment with TOF due to intolerance or adverse effect to MTX or LEF.

Effectiveness and predictors of clinical remission

At month 3, a statistically significant decrease in DAS28-ESR (from 5.58±1.13 to 3.44±1.49) and PDN requirement (from 91.04% to 57.46%) were observed. Table 2 shows DAS28-ESR, MTX requirement and PDN requirement at the time of initiating TOF and at three, six and twelve months of follow up. Remission was achieved in 38.06% at month 3 (n = 51). Table 3 compares patients who achieved remission versus patients in whom disease activity was not in remission at 3 months (univariate analysis). The group with no remission at 3 months had a significantly longer duration of disease, structural radiological damage, higher baseline DAS28-ESR and greater frequency in the previous use of bDMARDs. Figure 1 shows the probability of remission over time. The lineal model showed a significant difference in the probability of remission at the first 3 and 6 months (OR = 1.82, 95% CI 1.57-2.11; p <0.001) followed by a non-significant difference between 6 and 12 months (OR = 0.93; 95% CI 0.84-1.02; p = 0.109). In the multivariate lineal hierarchical regression model, previous use of bDMARD was significantly associated with a decrease in the probability of remission at three months (OR = 0.46, 95% CI 0.26 – 0.81; p = 0.008).

Table 1 Characteristics of the patients at the time of initiation of tofacitinib treatment.

	Total (n=134)
Female gender, n (%)	102 (76.12)
Age in years, median (IQR)	63 (55-70)
Comorbidities, n (%)	
Hypertension	64 (48.48)
Diabetes	9 (6.82)
Dyslipidemia	28 (21.21)
Smoking history	
ex-smoker	26 (19.40)
never a smoker	94 (70.15)
current smoker	10 (7.46)
unknown	4 (2.99)
Years of disease duration, median (IQR)	8 (4-18)
Laboratory, n (%)	
Rheumatoid factor [+]	116 (86.57)
Anti-citrullinated peptide antibodies [+]	110 (82.09)
Antinuclear antibody (ANA)	29 (21.64)
Radiological joint damage, n (%)	98 (73.13)
DAS28-ESR >5.1, n (%)	94 (70.1)
Prior treatment resulting in inadequate response, n (%)	
Methotrexate	132 (98.51)
Lefunomide	107 (79.85)
Previous biologic therapy, n (%)	54 (40.29)
1	38 (28.35)
2 or more	16 (11.94)
TNF inhibitor	44 (32.83)
Non-TNF inhibitor	22 (16.42)

Duration of treatment

The median duration of treatment with TOF was 12 months (IQR 7-24). Treatment persistence was 94.78% at 3 months, 82.84% at 6 months and 66.42% at 12 months. Table 4 compares baseline characteristics of patients receiving TOF monotherapy versus combination therapy at 12 months. At baseline, 88 patients received MTX associated with TOF and at 1 year 37 patients were on TOF monotherapy. A significant difference in median age was found in the TOF monotherapy group (68 years [IQR 63-72] versus 58.5 years [IQR 47-69], p = 0.009) and a trend for lower frequency of anti-CCP but not statistically significant. Further, those patients not able to discontinue concomitant therapy had a trend for higher frequency of anti-CCP.

Adverse events

AEs were identified in 14.1% (n = 19) of 134 patients, serious AEs in 1.5% (n = 2), serious infections in 1.5% (n = 2), discontinuations because of adverse events in 7.5% (n = 10) and no death were reported.

Table 2 Disease activity (DAS28-ESR), methotrexate (MTX) requirement, prednisone (PDN) requirement at baseline (at the time of initiating TOF) and follow-up (3, 6 and 12 months).

	Baseline (n = 134)	3 months (n = 134)	p-value*	6 months (n = 122)	p-value*	12 months (n = 79)	p-value*
DAS28-ESR, Mean±SD	5.58±1.13	3.44±1.49	< 0.0001	3.07±1.29	< 0.0001	2.71± 0.99	0.1166
MTX, n (%)	88 (65.67)	86 (64.18)	0.4795	69 (56.56)	0.0117	42 (53.16)	0.625
MTX dose, Mean±SD	10.99±8.41	10.15±8.18	0.0014	9.07±8.81	0.0407	8.54±8.95	0.9589
PDN, n (%)	122 (91.04)	77 (57.46)	< 0.0001	42 (34.43)	< 0.0001	18 (22.78)	0.3438
PDN dose, Mean±SD	7.89±4.55	3.46±3.48	<0.0001	1.89±2.93	<0.0001	1.11±2.21	0.1307

SD, standard deviation; *p value compared with the previous period.

Table 3 Univariate comparison at baseline between groups according to response after 3 months of tofacitinib therapy.

	Remission at month 3 (n=51)	Activity at month 3 (n=83)	p-value
Female gender, n (%)	40 (78.4)	62 (74.7)	0.623
Age in years, median (IQR)	63 (55-69)	63 (4-70)	0.992
Smoking history, n (%)	15 (29.4)	21 (25.3)	0.82
Disease duration in years, median (IQR)	5 (3-9)	12 (6-20)	0.0002
Laboratory, n (%)			
Rheumatoid factor [+]	43 (84.3)	73 (89)	0.549
Anti-citrullinated peptide antibodies [+]	40 (78.4)	70 (84.3)	0.387
Radiological joint damage, n (%)	31 (60.7)	67 (80.7)	0.011
DAS28-ESR, mean (SD)	5.31 (± 1.27)	5.74 (± 1.00)	0.018
DAS28-ESR >5.1, n (%)	31 (60.7)	63 (75.9)	0.063
Concomitant treatment, n (%)			
Methotrexate	29 (56.8)	59 (71)	0.092
Prednisone	48 (94.1)	74 (89.1)	0.329
Previous biologic therapy, n (%)	14 (27.4)	40 (48.1)	0.017
1	10 (19.6)	28 (33.7)	0.059
2 or more	4 (7.8)	12 (14.4)	0.059
TNF inhibitor	10 (19.6)	34 (40.9)	0.011
Non-TNF inhibitor	7 (13.7)	15 (18)	0.51

IQR, interquartile range; SD, standard deviation

Table 4 Comparison of baseline characteristics between tofacitinib (TOF) monotherapy at 12 months and combination therapy (TOF + methotrexate or MTX)

	Total	TOF monotherapy	TOF + MTX	p-value
n (%)	79 (100)	37 (46.8)	42 (53.2)	-
Female gender, n (%)	58 (73.4)	28 (75.7)	30 (71.4)	0.67
Age in years, median (IQR)	64 (54-71)	68 (63-72)	58.5 (47-69)	0.009
Smoking history, n (%)	19 (24.1)	10 (27.0)	9 (21.4)	0.561
Disease duration in years, median (IQR)	9 (5-19)	9 (5-18)	9.5 (5-19)	0.6758
Laboratory, n (%)				
Rheumatoid factor [+]	67 (84.8)	32 (86.5)	35 (83.3)	0.697
Anti-citrullinated peptide antibodies [+]	63 (79.8)	27 (73.0)	36 (85.7)	0.16
Radiological joint damage, n (%)	57 (72.12)	28 (75.7)	29 (69.1)	0.512
DAS28-ESR, mean (SD)	5.45 (± 1.24)	5.66 (± 1.43)	5.27 (± 1.03)	0.2404
DAS28-ESR>5.1, n (%)	49 (62.0)	22 (59.5)	27 (64.3)	0.659
Previous bDMARD, n (%)	78 (98.7)	36 (97.3)	42 (100)	0.284

IQR, interquartile range; SD, standard deviation

Serious infections (requiring hospital admission) occurred in 2 patients (one case of septic arthritis in the 11-mg group and 1 case of typhlitis in the 11-mg group). No serious infections occurred in 8 patients (5 cases of herpes zoster [HZV] in the 11-mg group, 2 cases of HZV in the 5-mg BID group, and 1 urinary tract infection in the 11-mg group. Of the 7 patients who had HZV, only 1 was simultaneously receiving PDN, 5 occurred in the first six months of therapy and the 2 remaining after 6 months. All cases were 1 dermatome and none

ophthalmic. Latent tuberculosis was diagnosed in 1 patient (0.7%) however active tuberculosis was not observed. No opportunistic infections and no cases of malignancy were reported. Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis were not observed.

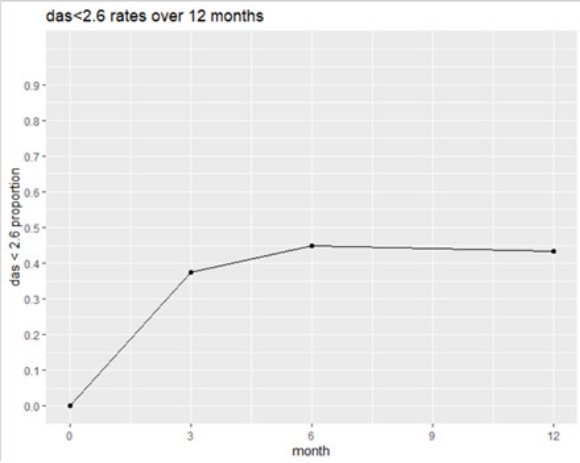

Figure 1 Evolution of the probability of remission over time.

Changes in laboratory test results were found in 4 patients. Increases in cholesterol levels (grade 1) in 1 case in the 11-mg group, leucopenia (grade 2) in 1 case in the 5-mg BID group, thrombocytopenia (grade 1) in 1 case in the 5-mg BID group and lymphopenia (grade 1) in the 11-mg group. Bicytopenia occurred in a patient who also received LEF which was discontinued and continues to date with TOF. Finally, digestive intolerance occurred in 2 patients, vitiligo exacerbation in 1, and pharmacoderma leading to discontinuation of TOF in 1.

TOF discontinuation occurred in 28 patients (20.9%); 17 of them discontinued it during the first year of follow-up. In months 0 to 3, 4 patients discontinued therapy (owing to lack of effectiveness in two patients, and AEs in two patients). In the second trimester, 8 patients stopped TOF (lack of effectiveness in 1 patient and AEs in 7 patients). Finally, at the end of the first year of follow-up 5 patients had discontinued TOF (lack of effectiveness in four patients, AEs in one patient). AEs were the most common reason for discontinuation.

Discussion

Observational studies evaluating treatments in routine clinical practice and outside the highly controlled setting of RCTs are the main source of real-world data.[23] In the present study we describe the effectiveness, safety and survival of TOF therapy in RA patients from Argentina as well as the patients' features that could be associated with therapeutic success in the short term follow-up.

Regarding clinical effectiveness, the median DAS28-ESR at month 3 and 6 showed discrepancy with phase 3 and long-term extension studies in LatAm since DAS28-ESR LDA and DAS28-ESR remission were lower than those observed in our study.[13] In a 6-month observational study from Japan (n=70) higher results for DAS28-ESR LDA (40%) and DAS28-ESR remission (21.4%) were obtained.[16] We consider that the difference found in our study is due to inherent limits of observational studies. Retrospective cohort studies are often assumed to have more bias since the study operations, data collected, data entry, and data quality assurance, were not planned ahead of time. Comparing across institutions and across different time periods introduces additional levels of bias. In this sense, we prefer to be cautious when interpreting this finding.

It is widely accepted that remission is the main therapeutic target for patients with RA, with low disease activity (LDA) as the best possible alternative, and that a treat-to-target (T2T) strategy should be applied when treating patients with RA.[24] If there is no improvement within three months after the start of treatment or the target has not been reached in 6 months, therapy should be adjusted. In our study, patients that remained active at three months with TOF therapy tended to have a longer disease duration of RA, structural radiological joint damage, high baseline disease activity and had received prior treatment with a bDMARD. Although more studies are needed, these findings could lead to improved outcomes by stratifying the risk of response to TOF (or tsDMARDs) based on the presence or absence of these potential prognostic factors. The first 3-6 months of TOF therapy represented the time interval where remission was possible. Beyond 6 months, patients not achieving this goal or LDA should be switched.

Almost 34% of our patients started on TOF monotherapy but in the short-term follow-up, almost half of the patients (45%) discontinued MTX. A study analyzing the data from the CORRONA registry found that among patients who initiated TOF (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.[25] In a prospective, observational Japanese study (n=113) the concomitant MTX use was 72.6% and in a retrospective, observational study from the same country (n=70) the concomitant MTX use was 68.6%.[15,16] Unlike the US registry, the RWS evidence of TOF monotherapy in LatAm shows results equal to or even lower than our cohort (10-41%).[19–21] Difference between US data and LatAm data could be the source of information to evaluate results (claims data versus medical records).

In RWS literature, we did not find TOF monotherapy as a therapeutic goal in the short-term follow-up being this feasible in patients who were able discontinue corticosteroids first (e.g. at 3-6 months). Furthermore, we found in our study that patients who discontinued MTX at 12 months were elderly. RCTs showed TOF to be similarly efficacious in young and elderly groups but due to comorbidities, a numerically higher risk of serious AEs and discontinuations due to AEs compared with younger patients was observed.[26] Evidence for the effectiveness of TOF in elderly patients with RA is scarce and more studies are needed in this regard.

In our cohort, treatment persistence was 82.84% at 6 months and AEs were the main reason for discontinuation. In the ORAL Sequel long-term extension study (n=4481) evaluating the safety and efficacy of TOF 5 mg and 10 mg BID for up to 9.5 years, 52% discontinued TOF with a median time to discontinuation of 4.9 years and the main reason for discontinuation was due to AEs (24%) and lack of effectiveness (4%).[11] A retrospective analysis from Switzerland (n=144) with a mean follow-up of 1.22 years describes lack of effectiveness as the main cause of TOF discontinuation.[27] Iwamoto et al. (n=70) described that at 6 months, 82.9% of patients were still receiving TOF and lack of effectiveness was also the most frequent cause of discontinuation.[16] TOF persistence in Canada, using data captured by the eXel support program, was estimated as 62.7% after 1 year and 49.6% after 2 years. Moreover, TOF persistence was higher in bDMARD-naive (vs bDMARD-experienced) and older patients.[28]

Infectious diseases and TB are more prevalent in LatAm than in Europe and the US, and need to be taken into consideration when selecting RA therapies in this region.[29,30] AEs were registered in 14.1% and as with other RCTs, infection was the most frequent AEs seen in our study. Among infection types, HZ was the most common and the incidence was similar to than seen in previous studies. A

comparative study evaluated the risks of HZ and herpes simplex virus (HSV) infection among RA patients with no history of HZ or HSV infection, initiating TOF or bDMARDs and increased HZ risk was associated with older age, female gender, prednisone >7.5 mg/day, prior outpatient infection and a larger number of hospitalizations.[31] These risk factors were found in our patients although none had a previous history of HZ. There were no records of active TB in our cohort as could also be observed in phase 3 and long-term extension studies in LatAm patients. No opportunistic infections, malignancy and no cases of thrombosis were reported although a longer follow-up is needed to draw definite conclusions in this regard.

Conclusions

Clinical remission obtained at month 3 was similar to other RWS studies. Clinical response achieved at 3-6 months might depend on the presence or absence of prognostic factors. Previous use of bDMARDs is a risk factor for a decrease in the probability of remission at 3 months. TOF monotherapy at 12 months might be associated with advanced age. More studies are needed to confirm these assumptions.

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Conflicts of interest

The authors declare no conflicts of interest.

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