Real-world effectiveness of tofacitinib in patients with rheumatoid arthritis: a prospective observational study

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Abstract

Objective

Tofacitinib is an approved treatment for rheumatoid arthritis (RA), but data on its use in the "real-world" are limited. We sought to analyse tofacitinib drug survival in the Israeli registry and compare it to other biologic agents.

Methods

We included RA patients treated with tofacitinib, etanercept, golimumab, tocilizumab, or abatacept between 2010-2019. The primary endpoint was event-free survival (EFS), defined as the time from treatment initiation to a treatment failure event from any cause (i.e. inefficacy or intolerability). EFS was compared between agents using Cox regression and Kaplan-Meier analysis, stratifying patients by treatment line.

Results

A total of 964 eligible treatment courses were included (tocilizumab [325], etanercept [284], abatacept [127], tofacitinib [139], and golimumab [109]). In a univariate analysis, EFS with tofacitinib in the complete cohort was similar to etanercept, golimumab, and abatacept but was lower than tocilizumab) 3-year EFS 43% vs. 53%, HR 0.65). In a multivariable analysis, tofacitinib was similar to all other drugs, except for etanercept, which was inferior (HR 1.70); advanced treatment line was also associated with greater risk for failure (HR 1.64). In a univariable analysis stratified by the treatment line, tofacitinib had similar or better drug survival than other agents in the first and second lines. In the third line and beyond, tocilizumab had a higher EFS compared to tofacitinib (HR 0.57).

Conclusion

Drug survival with tofacitinib is related to treatment line. Early introduction is associated with similar or better survival than other agents, whereas tocilizumab was superior in the third line or later.

Key words

rheumatoid arthritis, tofacitinib, disease-modifying anti-rheumatic drug, drug survival, safety

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Introduction

Disease modification is the mainstay of rheumatoid arthritis (RA) treatment. The arsenal of disease-modifying anti-rheumatic drugs (DMARDs) for RA treatment is continuously expanding. It includes conventional synthetic DMARDs, biologic (b) DMARDs, and the recently developed class of targeted synthetic DMARDs (1). Tofacitinib is an oral small-molecule inhibitor that reversibly inhibits Janus-activated kinase (JAK)-dependent cytokine signaling, thereby reducing inflammation. Its mechanism provides an innovative approach for modulating the immune and inflammatory responses in patients with rheumatoid arthritis (RA) (2, 3).

Tofacitinib, alone or in combination with methotrexate, has been shown as an effective and safe therapy for RA patients in a series of phase II, phase III randomised controlled trials (RCTs) and retrospective studies (4-16). Nevertheless, limited "real-world" data, in the form of scientific abstracts, is available on tofacitinib's efficacy and safety (17-19).

In 2014, Israel was one of the first countries to approve tofacitinib for RA treatment, preceding the European Medicines Agency (EMA) by three years. Initially approved for patients after failure of TNF-α-inhibitors, the indication was expanded in 2016 to biologic-treatment naïve with moderate to severe RA. Given the early introduction of tofacitinib, the Israeli registry is rich in data on this drug and may be useful for studying questions related to drug efficacy and tolerability.

Using prospectively collected data from the Israeli registry, we sought to explore the drug survival (*i.e.* drug retention rates) of tofacitinib in RA in comparison with other bDMARDs as well as the factors influencing it.

Materials and methods

Patients

This is a prospective cohort study analysing data from the Israeli registry. The registry includes data on inflammatory rheumatic diseases, reported by six Israeli medical centres. The registry is updated biannually and contains prospectively collected information regarding patient demographics, comorbidities, assessment of disease activity, drug therapies for RA, and adverse effects resulting in treatment cessation. The research protocol was approved by the Medical Center's Helsinki committee (approval no. 0332-10 TLV).

Inclusion criteria were adults (age ≥18 years), signing informed consent, meeting the American College of Rheumatology for diagnostic criteria for RA, and treated with tofacitinib or other accepted bDMARDs (etanercept, golimumab, abatacept, and tocilizumab) for treatment of RA, between 2010 and 2019.

The patients were evaluated at the initial visit (baseline) and every six months thereafter. Tofacitinib was compared to bDMARDs described in the inclusion criteria. Etanercept has been chosen as it is a well-established TNFα inhibitor, golimumab as a newer anti-TNF, and abatacept and tocilizumab as bDMARDS with a different mode of action.

Definitions

Treatment course was defined as the period from treatment initiation until discontinuation from any cause (inefficacy or intolerance). Treatment duration with selected drugs could be as short as three months and reach a maximum of up to three years. More than one treatment course per patient was allowed in patients having been switched from one drug to another. Treatment courses without any follow up were excluded (Supplementary Fig. S1).

Endpoints

The primary endpoint was event-free survival (EFS), defined as the time from treatment initiation to a treatment failure event from any cause (inefficacy or intolerability). EFS reflects the drug's retention rate, *i.e.* the drug survival rate. Secondary outcomes were drug discontinuation due to inefficacy and intolerability.

Statistical analysis

Standard descriptive statistics were used to analyse the baseline characteristics. Missing values were kept as a separate level. Continuous variables were categorised into three bins. The

Table I. Baseline characteristics.

Characteristic	Tofacitinib	Etanercept	TF *vs*. ET *p*-value	Golimumab	TF *vs*. GL *p*-value	Tocilizumab	TF *vs*. TC *p*-value	Abatacept	TF *vs*. AB *p*-value
Treatment course	139 (14%)	264 (28%)		109 (11%)		325 (34%)		127 (13%)	.
Sex									
Male	17 (12%)	56 (21%)	0.029	18 (17%)	0.362	65 (20%)	0.047	22 (16%)	0.298
Female	122 (88%)	208 (79%)	.	91 (83%)	.	105 (80%)	.	105 (84%)	.
BMI									
18.5-24.9	47 (37%)	77 (38%)	0.858	35 (39%)	0.82	96 (36%)	0.815	39 (42%)	0.302
25-34.9	67 (53%)	107 (53%)		48 (53%)		136 (51%)		40 (43%)	
≥35	13 (10%)	17 (8%)		7 (8%)		33 (12%)		14 (5%)	
Missing	12	63		19		60		34	
Year									
<2013	1 (1%)	154 (58%)	<0.001	51 (47%)	<0.001	188 (58%)	<0.001	19 (15%)	<0.001
2014-2015	44 (32%)	69 (26%)		30 (28%)		82 (25%)		66 (52%)	
2016-2019	94 (68%)	41 (16%)		28 (26%)		55 (17%)		42 (33%)	
Median age at course (y, range)	66 (21-88)	59 (17-87)	0	56 (19-81)	0	59 (17-87)	0	56 (19-81)	0.001
Median age at diagnosis (y, range)	51 (2-77)	50 (1-87)	0.287	43 (1-72)	0.002	57 (1-79)	0.016	45 (1-73)	0.01
Median disease duration (y, range)	13 (0.5-50)	7 (0.5-54)	0	8 (0.5-53)	0.022	10 (0.5-52)	0.029	11 (0.5-51)	0.305
Concomitant use of MTX									
No	34 (25%)	55 (21%)	0.449	23 (22%)	0.547	82 (25%)	0.907	36 (27%)	0.489
Yes	105 (75%)	209 (79%)		86 (78%)		243 (75%)		91 (73%)	

TF: tofacitinib; ET: etanercept; GL: golimumab; AB: abatacept; TC: tocilizumab; MTX: methotrexate; Y: year.

Table II. Line of therapy by agent.

Line biol.	Total	Tofacitinib	Etanercept	TF *vs*. ET *p*-value	Golimumab	TF *vs*. GL *p*-value	Tocilizumab	TF *vs*. TC *p*-value	Abatacept	TF *vs*. AB *p*-value
1	364 (37%)	31 (17%)	179 (66%)	<0.001	48 (44%)	0.007	86 (26%)	0.000	20 (15%)	0.730
2	239 (25%)	28 (19%)	49 (20%)	.	17 (16%)	.	117 (35%)	.	28 (22%)	.
3	160 (17%)	28 (20%)	22 (9%)	.	16 (14%)	.	65 (21%)	.	29 (23%)	.
4	98 (11%)	22 (18%)	9 (3%)	.	9 (8%)	.	35 (11%)	.	23 (19%)	.
5+	103 (11%)	30 (26%)	5 (2%)	.	19 (17%)	.	22 (7%)	.	27 (22%)	.
Total	964 (100%)	139 (100%)	264 (100%)		109 (100%)		325 (100%)		127 (100%)	

TF: tofacitinib; ET: etanercept; GL: golimumab; AB: abatacept; TC: tocilizumab.

Mann-Whitney and Chi-squared tests were used to compare differences between patient characteristics and drugs. We constructed univariable and multivariable Cox regression models for EFS. Variables considered in the univariable analysis were sex, year of course, age at course, disease duration before course, BMI, DMARD, and concomitant use of methotrexate at time of course. Covariates meeting statistical significance ($p<0.05$) were introduced into the multivariable analysis. Interactions between treatment line and bDMARDs and methotrexate and bDMARDs were considered in the univariable analysis. EFS probabilities at 1, 2 and 3 years from treatment course were calculated using Kaplan-Meier estimates. Two-tailed *p*-values of 0.05 or less was considered to be statistically significant. All statistical analysis was performed with SPSS, v. 25.

Results

Population characteristics

The demographic and clinical characteristics of study participants are presented in Table I. The data fulfilling the inclusion criteria (Suppl. Fig. S1) from the registry included 634 patients (510 females, 80%) with a total number of 964 courses (325 with tocilizumab [34%], 264 etanercept [28%], 127 abatacept [13%], 139 Tofacitinib [14%], and 109 golimumab [11%]; Table II). The median age at diagnosis was 51 years in the tofacitinib group, similar to etanercept ($p=0.287$) but higher than all other groups. Patients in the Tofacitinib group were older at treatment initiation (median age 66 years) compared to all other treatment groups ($p<0.001$). Tofacitinib courses were given in more recent years compared to all other bDMARDs ($p<0.001$). The median duration from RA diagnosis to treatment initiation was longest with tofacitinib and abatacept (median 13 and 11 years, respectively); other groups had a statistically significant shorter disease duration compared to tofacitinib. Similar rates of concomitant methotrexate administration were observed across all groups, ranging from 73–79%.

The proportion of treatment courses where tofacitinib was used as first-line therapy was 17%, similar to abatacept (15%) ($p=0.730$). Etanercept (66%), golimumab (44%), and tocilizumab (26%) were all more likely to be given as first-line. Overall, the tofacitinib

Table III. Univariate analysis for drug survival for all patients.*

Treatment line	Drug	*p*-value	HR for drug discontinuation (95% CI)	1-y EFS	2-y EFS	3-y EFS
All lines combined	Tofacitinib		1 (ref)	61%	48%	43%
	Etanercept	0.412	1.13 (0.84-1.53)	57%	46%	35%
	Golimumab	0.805	0.96 (0.66-1.38)	65%	50%	37%
	Tocilizumab	0.006	0.65 (0.48-0.88)	73%	62%	53%
	Abatacept	0.791	1.05 (0.74-1.49)	64%	47%	30%
Line #1	Tofacitinib		1 (ref)	79%	70%	59%
	Etanercept	0.033	2.10 (1.06-4.14)	60%	47%	34%
	Golimumab	0.580	1.25 (0.56-2.78)	76%	64%	50%
	Tocilizumab	0.805	0.96 (0.42-1.95)	80%	71%	63%
	Abatacept	0.482	1.41 (0.54-3.65)	75%	57%	46%
Line #2	Tofacitinib		1 (ref)	73%	53%	53%
	Etanercept	0.333	1.44 (0.69-2.99)	51%	49%	44%
	Golimumab	0.139	1.94 (0.81-4.68)	43%	32%	22%
	Tocilizumab	0.615	0.84 (0.42-1.67)	72%	63%	55%
	Abatacept	0.776	1.13 (0.48-2.67)	73%	46%	36%
Line #3+	Tofacitinib		1 (ref)	48%	36%	32%
	Etanercept	0.832	1.06 (0.63-1.76)	52%	40%	27%
	Golimumab	0.583	0.87 (0.53-1.44)	58%	40%	27%
	Tocilizumab	0.006	0.57 (0.38-0.85)	69%	55%	46%
	Abatacept	0.484	0.86 (0.57-1.31)	58%	44%	23%

* Full univariable analysis provided in the Supplementary file.
HR: hazard ratio; CI: confidence interval; EFS: event-free survival.

treatment line distribution was well balanced, with approximately 20% for each line (Table II).

Primary outcome: event-free survival

Median follow-up for EFS was 12.7 months (range: 0.03–109.5). In univariable analysis, EFS with tofacitinib in the complete cohort was similar to etanercept, golimumab, and abatacept but was lower than tocilizumab (3-year EFS 43% *vs*. 53%, HR 0.65 [95% CI: 0.48–0.88]). When analysing the additional variables considered in the univariable analysis, there was an association between advanced treatment line (p=0.018), treatment courses given in more recent years (p<0.001), and concomitant use of prednisone (p=0.036), and decreased EFS. No association was found with sex, age at treatment course initiation, BMI, and concomitant use of methotrexate (Table III, Suppl. Table S1). In the multivariable analysis (Table IV), among bDMARDs studied, only tocilizumab had an increased risk for an EFS event compared to tofacitinib (HR 1.70 [95% CI: 1.22–2.37]). Advanced treatment line and more recent treatment course years were also associated with lower EFS.

Table IV. Multivariable analysis for drug survival.

	p-value	HR (95% CI)
Treatment line		
First (1)		1
Second (2)	0.187	1.19 (0.92-1.54)
Third+ (≥3)	<0.001	1.64 (1.31-2.07)
Year at course		
<2013		1
2014-2019	<0.001	1.50 (1.22-1.84)
Agent		
Tofacitinib		1
Tocilizumab	0.338	0.85 (0.61-1.18)
Etanercept	0.002	1.70 (1.22-2.37)
Abatacept	0.706	1.07 (0.75-1.52)
Golimumab	0.269	1.24 (0.85-1.81)

HR: hazard ratio; CI: confidence interval; EFS: event-free survival.

bDMARD and methotrexate administration did not interact with respect to EFS. We did, however, find interactions between bDMARD and concomitant use of prednisone and bDMARD and treatment line (Table III, Suppl. Table S2). The deleterious association of prednisone was most pronounced in patients treated with tocilizumab (HR 1.50 [95% CI: 1.06–2.12], p=0.022) and tofacitinib (HR 1.63 [95% CI: 0.97–2.74], p=0.067). In the first-line setting, tofacitinib has similar EFS to other treatments (Fig. 1A), except etanercept, which was associated with a greater risk for the primary event (HR 2.10 [95% CI: 1.06–4.14], p=0.033; 1, 2 and 3 years EFS with tofacitinib was 79%, 70%, and 59%; corresponding EFS with etanercept was 60%, 47%, 34%). However, the analysis might not have been powered to detect differences, given the low number of tofacitinib treatment courses in the first line. The risk of an EFS event overlapped between tofacitinib and all other treatments given as second-line therapy (Fig. 1B). In third-line therapy, tocili-

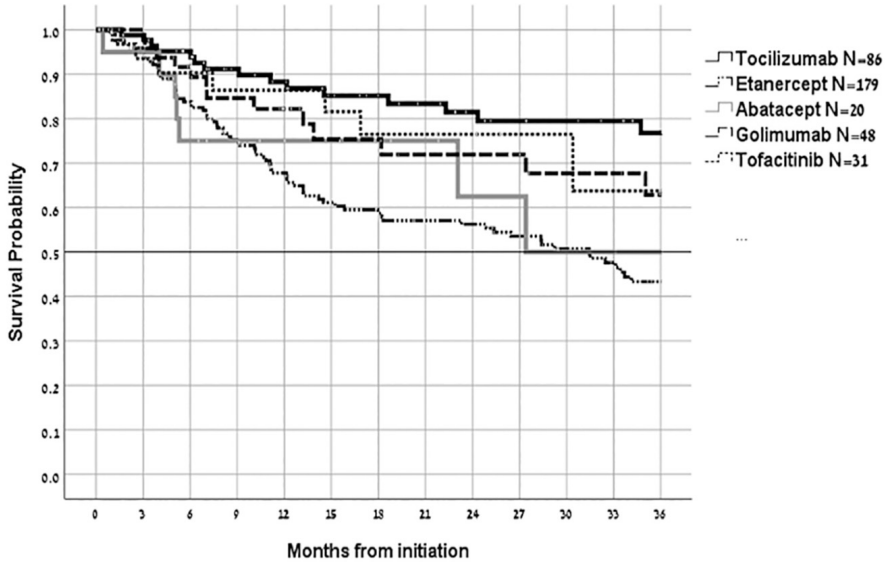

Fig. 1A. Event-free survival at first line.

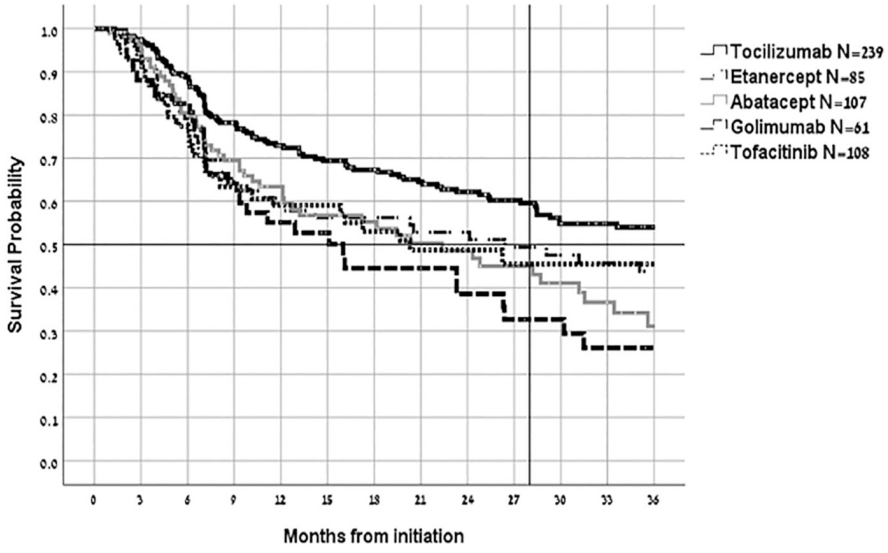

Fig. 1B. Event-free survival at second Line +.

zumab had a lower risk compared to tofacitinib (3-year EFS 46% *vs*. 32%; HR 0.57 [95% CI 0.38–0.85] *p*=0.006). There was no benefit with any other drug (Fig. 1B).

Secondary outcome: inefficacy and adverse events

Inefficacy was the leading cause of discontinuation of all of the studied drugs (Table V). From a total of 964 treatment courses, 379 (39%) ended because of inefficacy. Only 83 (9%) of discontinuation events were due to adverse effects. In the tofacitinib group, we observed the same trend, with 11 (8%) discontinuation events due to adverse events, which were mostly dermatologic (3/11; 2 related to Varicella-zoster virus infection and 1 to pruritus and swelling).

Discussion

This "real-world" study found that tofacitinib is primarily administered as second-line therapy or later. In this setting, tofacitinib had similar or superior EFS (*i.e*. drug survival) to other bDMARDs, except for tocilizumab, which had better drug survival in first-line and third-and beyond line therapy. Overall, the timing of bDMARD introduction (*i.e*. line of therapy) is the strongest predictor of drug survival. Finally, tofacitinib is well tolerated and has a good safety profile.

"Real-world" data on tofanitinib are limited. Two retrospective analyses from the US administrative claims database have been reported. Harnett *et al*. found that in a cohort of RA patients treated with bDMARD, tofacitinib was more likely to be prescribed later than other bDMARDs (14). Nevertheless, it had at least comparable persistence and adherence with lower adjusted mean RA-related total costs. Notably, in contrast to our population, where tofacitinib was given together with methotrexate in the majority of patients, in the US database, it was primarily prescribed as monotherapy. Smith *et al*. studied the same registry to compare tofacitinib to other bDMARDs but focused on earlier administration of the drug in RA patients treated between

Table V. Inefficacy and adverse events leading to drug discontinuation.

	Total	Tofacitinib	Etanercept	TF *vs*. ET *p*-value	Golimumab	TF *vs*. GL *p*-value	Tocilizumab	TF *vs*. TC *p*-value	Abatacept	TF *vs*. AB *p*-value
Inefficacy event										
No	585 (61%)	89 (62%)	147 (56%)	0.112	63 (59%)	0.359	218 (67%)	0.523	68 (54%)	0.105
Yes	379 (39%)	50 (38%)	117 (44%)	.	46 (41%)	.	107 (33%)	.	59 (46%)	.
Adverse event										
No	881 (91%)	128 (93%)	228 (86%)	0.103	102 (94%)	0.806	302 (92%)	0.846	121 (96%)	0.325
Yes	83 (9%)	11 (7%)	36 (14%)	.	7 (6%)	.	23 (8%)	.	6 (4%)	.

TF: tofacitinib; ET: etanercept; GL: golimumab; AB: abatacept; TC: tocilizumab.

2014 and 2017. Again, tofacitinib was more frequently prescribed as monotherapy than adalimumab or etanercept while having comparable persistence and adherence to the other bDMARDs (20). Caporali *et al*. reviewed data from 24 real-world studies, but many were published only in an abstract form (13). They conclude that treatment persistence and adherence to tofacitinib are good overall and similar to those seen for bDMARDs. Overall, our results, together with previous publications, show that patients on tofacitinib enjoy a relatively long-disease free duration, which is comparable or better than other bDMARDs. Moreover, it is well-tolerated, and patient adherence is similar to other bDMARDs.

Whether the early introduction of tofacitinib benefits patients is not clear. In the current analysis, only a few patients received tofacitinib as first-line therapy; hence, comparison with other drugs was limited. Though, when considered in the multivariable analysis, including both bDMARDs and treatment line number (Table IV), earlier treatment line was associated with better EFS. Therefore, it is likely that tocilizumab's use in first-line therapy would result in better survival with the drug. In second-line therapy, we find that tocilizumab is comparable to the majority of bDMARDs. Therefore, the selection of second-line treatment should be driven by the safety profile of the drug. The good tolerability and safety, as reflected by our results as well as other studies (21, 22), suggest that tofacitinib is a worthy candidate. In our study, only mild side adverse were reported for tofacitinib, mainly dermatologic (n=3, 38%), two of them with herpes zoster.

The interpretation of factors associated with drug survival (*i.e*. EFS) may be confounded by interactions in a cohort such as ours. These interactions include the significant impact of bDMARDs in different treatment lines, as well as the treatment year. Treatment year may affect drug survival since agents have been introduced in different years, and the timing of exposure to treatments has shifted accordingly. Since tofacitinib was rarely used before 2013, we could not analyse this interaction. However, treatment year is accounted for in the multivariable analysis (Table IV). Another potential interaction is between bDMARDs and concomitant use of methotrexate (23), which was not found to impact drug survival of the drugs studied significantly. One of the possible explanations of the absence of the effect of methotrexate in our study may be due to the fact that we did not include strongly immunogenic biologics such as infliximab or adalimumab.

Conclusion

In this prospective observational study, the "real-world" experience with tofacitinib was encouraging. Drug survival (*i.e*. EFS) was comparable or better to other bDMARDs but was also dependent on the timing of tofacitinib introduction. Our data suggest that in first-line therapy, tofacitinib is equivalent to or better than other bDMARDs. In more advanced therapy lines (≥3), tofacitinib had similar EFS to other agents, except tocilizumab, that was associated with longer drug survival. Importantly, tofacitinib had a low rate of adverse events leading to drug discontinuation. Overall, our results indicate that tofacitinib in the "real-world" is a viable RA treatment, recapitulating its efficacy and tolerability, as observed in clinical trials.

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