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Determinants of tofacitinib discontinuation in adult patients with rheumatoid arthritis during long-term extension studies up to 9.5 years

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Abstract

Objectives: To examine determinants of tofacitinib discontinuation due to voluntary (i.e. patient-driven) or involuntary reasons (i.e. protocol mandated) in long-term extension (LTE) studies of patients with RA to inform clinical practice, clinical study execution and data capture.

Methods: This post hoc analysis used pooled data from patients receiving tofacitinib 5 or 10 mg twice daily (BID) in LTE studies. Outcomes included time to voluntary/involuntary discontinuation (and baseline predictors), including by geographic region. Exposure-adjusted event rates (EAERs) were calculated for adverse events (AEs), serious AEs (SAEs) and discontinuations due to AEs/SAEs.

Results: Of 4967 patients, 2463 (49.6%) discontinued [1552/4967 (31.2%) voluntarily, 911/4967 (18.3%) involuntarily] and 55 (1.1%) died over the course of 9.5 years. When involuntary discontinuation was present as a competing risk for voluntary discontinuation, patients who stayed on combination therapy and with higher patient-assessed pain were significantly more likely to discontinue for voluntary reasons ($P < 0.05$). Older patients, those enrolled in Asia, Europe or Latin America (*vs* USA or Canada) or with RF^+/anti-CCP^+ status were significantly less likely to discontinue for voluntary reasons ($P < 0.05$). Small numeric differences in disease activity were observed between geographic regions in patients who discontinued or completed the studies. EAERs were generally higher for tofacitinib 10 *vs* 5 mg BID, irrespective of discontinuation reason.

Conclusion: The factors associated with voluntary/involuntary discontinuation of tofacitinib suggest that treatment persistence in RA studies is partly predictable, which may be reflected in clinical practice. Applying these results may improve our understanding of attrition and inform future study design/execution.

Trial registrations: ClinicalTrials.gov (http://clinicaltrials.gov): NCT00413699 and NCT00661661.

Lay Summary

What does this mean for patients?
Rheumatoid arthritis (RA) is a disease that causes swollen and painful joints. Tofacitinib is a medicine used to treat RA. Long-term clinical studies of tofacitinib have lasted up to 9.5 years. Over that long time period, continued use of tofacitinib varied considerably, just like in real life. We found that we could partly predict why patients stop taking tofacitinib during these studies. A total of 4967 patients took tofacitinib in long-term clinical studies. In these studies, one in three decided to stop tofacitinib and one in five were told to stop tofacitinib by the study doctor when they met certain conditions that were explained in the study plan. Patients with self-assessed pain and patients taking tofacitinib with other RA medicines were more likely to decide to stop taking tofacitinib, as were patients in the USA and Canada (when compared with those in Asia, Europe and Latin America). A patient's decision to stop tofacitinib was not strongly related to how well their disease was controlled. Side effects (adverse events) were not the main reason that patients decided to stop taking tofacitinib. Older patients and those with poor prognostic features (rheumatoid factor and anti-cyclic citrullinated protein antibodies in their blood) were less likely to decide to stop tofacitinib. This analysis will help researchers to better design RA clinical studies in the future and understand the influence of differences between countries in predicting who continues in a trial and who drops out.

Keywords: rheumatoid arthritis, clinical trials and methods, inflammation, DMARDs, pharmacology.

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Key messages

- In long-term extension studies, 31.2%/18.3% of tofacitinib-treated patients voluntarily/involuntarily discontinued over the course of 9.5 years.
- The rates of voluntary discontinuation in the long-term extension studies varied by region.
- Factors associated with tofacitinib discontinuation suggest treatment persistence in RA studies is partly predictable.

Introduction

Management of patients with RA has improved over recent decades due to earlier and more accurate diagnosis, earlier intervention following a treat-to-target approach and the introduction of DMARDs with different modes of action, including biologic DMARDs and targeted synthetic DMARDs [1, 2]. The time that a patient with RA remains on a given treatment (or 'persistence') is considered a reliable surrogate measure of the treatment's effectiveness, which encompasses efficacy, safety and tolerability, as patients who experience a lack of efficacy or adverse events (AEs) are more likely to discontinue and/or switch therapies [3–5]. Persistence with therapy has many contributing factors and it is important to better understand the reasons underlying treatment discontinuation and to identify patient-based predictors of treatment persistence in RA to inform routine clinical care and future RA study design/execution.

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Tofacitinib persistence has been previously evaluated in a post hoc analysis of data from long-term extension (LTE) studies up to 9.5 years [3, 6]. In that analysis, median drug persistence was ≈5 years, regardless of tofacitinib dose [3]. However, the analysis did not account for the differences in tofacitinib dose level, treatment duration and dropout rates during the index studies. Importantly, and as a unique feature of this report, while reasons for treatment discontinuation were previously reported, the most common being AEs (23.9%), lack of patient willingness to participate (10.1%), 'other' reasons (i.e. not classified; 6.2%) and lack/loss of efficacy (3.6%), persistence analyses were not stratified by reasons for discontinuation or whether the discontinuation was voluntary (i.e. at the patient's behest) or involuntary (i.e. mandatory as per protocol) [3]. The importance of these additional aspects of study persistence may inform future clinical study design and data capture with respect to expectations of treatment persistence (e.g. by geographic region), which in turn would impact sample size and power calculations, specifically in relation to long-term global safety surveillance studies.

In this post hoc analysis of data from the LTE studies [7, 8], we examined discontinuation of tofacitinib, stratified by voluntary and involuntary reasons for discontinuation. We aimed to explore patient or disease characteristics that may influence tofacitinib persistence, with a view to aiding prediction of which patients are more likely to derive benefit from tofacitinib treatment based on continued persistence, as well as to inform the design of future studies in RA where regional considerations may be important.

Methods

Patients and study design

Data were pooled from two multicentre, open-label LTE studies of tofacitinib in RA: ORAL Sequel (A3921024; NCT00413699), which was a global study, and Study A3921041 (NCT00661661), which was conducted only in Japan. Full details of both studies have been reported previously [7–9]. Both studies were ongoing (database not locked and data subject to change) at the time of this analysis, with cut-off dates of 2 March 2017 for ORAL Sequel and 24 April 2014 for A3921041.

Briefly, eligible patients were ≥18 (ORAL Sequel) or ≥20 (A3921041) years of age with RA based on the ACR 1987 revised criteria [10] and had completed a prior qualifying phase 1, 2 or 3 index study. Patients from the index studies initiated treatment in the LTE studies with tofacitinib 5 or 10 mg twice daily (BID). Most patients from phase 2 index studies initiated open-label treatment in the LTE studies with tofacitinib 5 mg BID, and most patients from phase 3 index studies initiated open-label treatment with tofacitinib 10 mg BID, with the exception of patients from China and Japan, who initiated treatment with tofacitinib 5 mg BID, per protocol.

Adjustments to stable background arthritis therapy, certain conventional synthetic DMARDs (csDMARDs) and glucocorticoids (GCs; ≤10 mg prednisone or equivalent/day) were permitted at the investigator's discretion for reasons of inadequate efficacy or tapering/discontinuation with disease improvement. Tofacitinib dose adjustments were also permitted during the LTE studies at the investigator's discretion for inadequate efficacy or safety reasons. In both LTE studies, protocol-mandated reasons for patients to withdraw from study participation included serious infection (requiring parenteral antimicrobial therapy or hospitalization), opportunistic infections (if judged significant by the investigator; ORAL Sequel only), other serious AEs (SAEs) or severe AEs (e.g. malignancy) and certain clinically significant confirmed laboratory abnormalities with two sequential measurements.

Both LTE studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, along with applicable local regulatory requirements and laws. Study protocols were approved by the institutional review board and/or independent ethics committee at each study centre. All patients provided written informed consent.

Endpoints and statistical analysis methodology

For the present analysis, data were included for patients who received an average tofacitinib daily dose of <15 mg (categorized as 5 mg BID) or an average daily dose of ≥15 mg (categorized as 10 mg BID). Patients who received stable doses of tofacitinib 5 or 10 mg BID during the LTE studies and who stayed on tofacitinib monotherapy or combination therapy with csDMARDs for the entire duration of the study, with the protocol-permitted ≤28-day break in csDMARD use, were further classified as 'stay-on monotherapy' or 'stay-on combination therapy' patients. In contrast, therapy patterns of those patients who adjusted monotherapy/combination therapy at the investigator's discretion during the LTE studies

were classified as 'mixed'. The full analysis set was defined as all patients treated with at least one dose of study treatment and who had at least one non-missing post-baseline value.

Demographics and baseline characteristics are reported for patients discontinuing tofacitinib due to voluntary and involuntary reasons. Voluntary reasons for discontinuation were defined as 'no longer willing to participate in the study', 'lost to follow-up', 'insufficient clinical response', 'other' and 'AE (non-protocol-mandated discontinuation due to AEs)'. Involuntary reasons for treatment discontinuation, as required by the study protocol, were defined as 'does not meet entrance criteria', 'protocol violation', 'withdrawn due to pregnancy' and 'AE' (only AEs related to protocol-mandated discontinuations, as specified in the 'Patients and study design' section above). Baseline values for demographics and characteristics were those of the index study.

All statistical analyses were carried out without any imputation for missing data and there was no multiplicity adjustment for *P*-values.

The cumulative incidence of voluntary discontinuation with involuntary discontinuation as a competing risk, and involuntary discontinuation with voluntary discontinuation as a competing risk, via the Aalen–Johansen estimation, was analysed for the time to tofacitinib discontinuation (defined as the difference between the end-of-study date and the first tofacitinib dose + 1 day), for all patients and according to the geographic region of the enrolment location [11].

Cox regression model–based analysis was used to assess the potential effects of baseline variables (Supplementary Table S1, available at *Rheumatology Advances in Practice* online) on tofacitinib discontinuation due to voluntary and involuntary reasons. Baseline covariates were initially screened in a univariate Cox analysis ($P < 0.1$) and were then selected in the final multivariable Cox regression model using backward selection, with $P < 0.15$ for stay criteria. Treatment as a factor was also included in the final model. Based on the final models, estimates of hazard ratios (HRs) with 95% CIs were generated.

Additionally, as one of the main objectives of this research was to investigate the potential impact of the baseline risk factors on voluntary discontinuation, a competing risk survival analysis for the univariate Cox analysis and the multivariable Cox regression was also performed, where voluntary discontinuation was the event of interest and involuntary discontinuation was specified as a competing risk based on the proportional subdistribution hazards model of Fine and Gray [12]. The same analysis was also performed for involuntary discontinuation with voluntary discontinuation as a competing risk.

The last available 28-joint DAS with erythrocyte sedimentation rate (DAS28-4ESR) scores and disease activity status (before discontinuation for patients who discontinued for voluntary and involuntary reasons or who completed) were presented by geographic region. The purpose of this analysis was to understand the level of disease activity at which patients chose to voluntarily withdraw from the study.

Treatment-emergent AEs and SAEs were summarized separately for patients who discontinued tofacitinib due to voluntary and involuntary reasons. Exposure-adjusted event rates (EAERs) of the number of patients with events per 100 patient-years were calculated for AEs and SAEs and discontinuations due to AEs and SAEs. EAERs were based on the number of unique patients with events per 100 patient-years over all patients' exposures between their first dose of tofacitinib and their last dose (excluding any temporary treatment breaks in-between).

Results

Patient demographics and baseline characteristics

A total of 4967 patients received tofacitinib 5 or 10 mg BID as monotherapy or in combination with csDMARDs in the LTE studies. Over a mean treatment duration of 3.5 years (median 3.5; maximum 9.4) and across tofacitinib treatment groups, 2463 (49.6%) patients discontinued treatment [1552/4967 (31.2%) patients discontinued due to voluntary reasons and 911/4967 (18.3%) discontinued for involuntary reasons] and 55/4967 (1.1%) patients died. For all patients receiving tofacitinib, across all regions, a higher proportion of patients discontinued due to voluntary reasons than involuntary reasons (Fig. 1).

Baseline characteristics were broadly similar between voluntary and involuntary discontinuation groups overall, although patients who discontinued due to voluntary reasons were marginally younger, with lower rates of cardiovascular disease (CVD) and seropositivity (RF^+/anti-CCP^+) than patients who discontinued for involuntary reasons (Table 1). For all patients receiving tofacitinib who discontinued due to voluntary or involuntary reasons, patients enrolled in the USA and Canada had the highest discontinuation rates among all regions. Patients who received the lower dose of tofacitinib had higher baseline CRP levels compared with those who received tofacitinib 10 mg BID, irrespective of the reason for discontinuation (Table 1).

Voluntary and involuntary reasons for discontinuation

Approximately half of all treated patients discontinued tofacitinib: overall, 31.2% of patients discontinued due to voluntary reasons (61.6% of all those discontinuing) and 18.3% due to involuntary reasons (36.2% of all those discontinuing) (Table 2). Reasons for voluntary and involuntary discontinuation are described in Table 2. In general, similar rates of discontinuation were observed between tofacitinib 5 or 10 mg BID treatment groups in terms of overall discontinuations or discontinuations for voluntary or involuntary reasons (Table 2).

In all patients who discontinued, numerical differences in reasons for discontinuation were observed between study sites in different geographic regions. However, AEs were the most common reason for discontinuation across all geographic regions, followed by patients no longer being willing to participate and for other reasons. There was a higher rate of involuntary discontinuations due to AEs in patients enrolled in Asia compared with the other regions (Supplementary Fig. S1, available at *Rheumatology Advances in Practice* online).

Time to discontinuation and factors affecting treatment discontinuation

The drug persistence estimate for all patients receiving tofacitinib and discontinuing for voluntary reasons, with involuntary discontinuation as a competing risk, or discontinuing for involuntary reasons, with voluntary discontinuation as a competing risk, is shown in Fig. 2A and C, respectively. The results demonstrate that over the course of the LTE studies, a higher percentage of patients discontinued tofacitinib

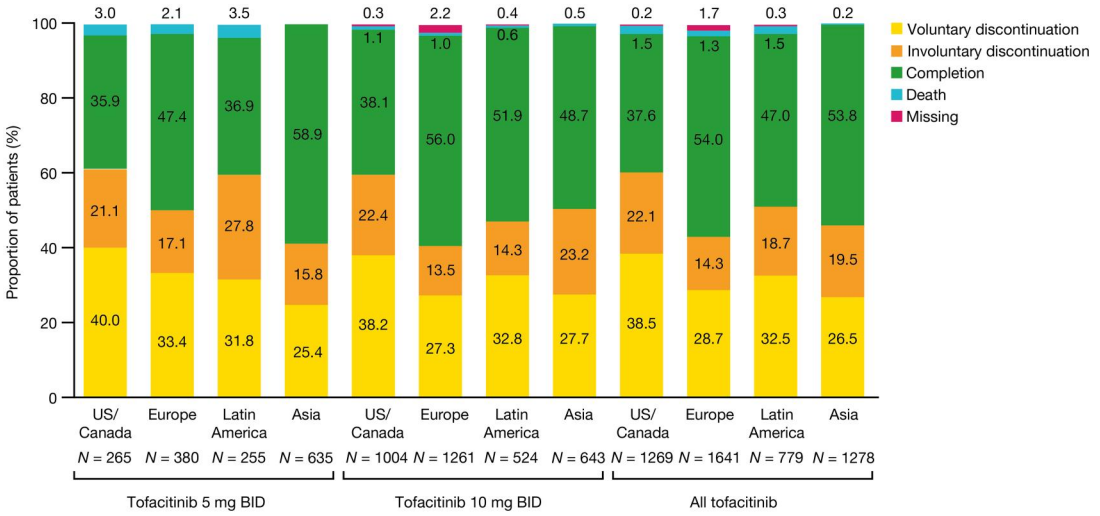

Figure 1. Proportion of voluntary and involuntary discontinuations, completions and deaths by geographic region

Table 1. Demographics and baseline characteristics at the start of the index study

Characteristics	Patients who discontinued tofacitinib						Patients who completed[a]
	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		All tofacitinib		All tofacitinib ($N = 2449$)
	Voluntary reasons ($n = 475$)	Involuntary reasons ($n = 292$)	Voluntary reasons ($n = 1077$)	Involuntary reasons ($n = 619$)	Voluntary reasons ($n = 1552$)	Involuntary reasons ($n = 911$)	
Age, mean (S.D.), years	53.4 (13.1)	55.3 (12.0)	52.2 (12.4)	56.7 (11.4)	52.5 (12.6)	56.2 (11.6)	52.3 (10.7)
Female, *n* (%)	399 (84.0)	241 (82.5)	903 (83.8)	480 (77.5)	1302 (83.9)	721 (79.1)	2016 (82.3)
Disease duration, years, mean (S.D.)	9.3 (8.4)	9.0 (7.9)	9.1 (8.0)	9.5 (8.7)	9.2 (8.1)	9.3 (8.5)	8.4 (7.4)
BMI category (kg/m^2), *n* (%)							
<25	240 (50.6)	138 (47.3)	410 (38.1)	242 (39.2)	650 (41.9)	380 (41.8)	1181 (48.2)
25–30	127 (26.8)	71 (24.3)	344 (31.9)	167 (27.0)	471 (30.4)	238 (26.2)	696 (28.4)
>30	107 (22.6)	83 (28.4)	323 (30.0)	209 (33.8)	430 (27.7)	292 (32.1)	572 (23.4)
Smoking status, *n* (%)							
Smoker/ex-smoker	136 (30.3)	109 (39.8)	396 (36.9)	249 (40.3)	532 (34.9)	358 (40.1)	827 (34.1)
Never smoked	313 (69.7)	165 (60.2)	678 (63.1)	369 (59.7)	991 (65.1)	534 (59.9)	1595 (65.9)
Geographic region, *n* (%)							
USA/Canada	106 (22.3)	56 (19.2)	383 (35.6)	225 (36.3)	489 (31.5)	281 (30.8)	480 (19.6)
Europe	127 (26.7)	65 (22.3)	344 (31.9)	170 (27.5)	471 (30.3)	235 (25.8)	914 (37.3)
Latin America	81 (17.1)	71 (24.3)	172 (16.0)	75 (12.1)	253 (16.3)	146 (16.0)	368 (15.0)
Asia	161 (33.9)	100 (34.2)	178 (16.5)	149 (24.1)	339 (21.8)	249 (27.3)	687 (28.1)
CRP (mg/dl), mean (S.D.)	8.6 (15.2)	9.2 (15.7)	7.1 (12.0)	7.6 (13.7)	7.6 (13.1)	8.1 (14.4)	7.2 (13.9)
DAS28-4ESR, mean (S.D.)	4.5 (1.6)	4.5 (1.6)	4.6 (1.6)	4.5 (1.6)	4.6 (1.6)	4.5 (1.6)	4.3 (1.6)
RF$^+$/anti-CCP$^+$, *n* (%)	313 (72.3)	220 (81.5)	588 (72.0)	415 (82.8)	901 (72.1)	635 (82.4)	1642 (82.6)
MTX use, *n* (%)	423 (89.1)	271 (92.8)	889 (82.5)	530 (85.8)	1312 (84.5)	801 (88.0)	2032 (83.0)
GC use, *n* (%)	267 (56.2)	166 (56.8)	594 (55.2)	373 (60.4)	861 (55.5)	539 (59.2)	1311 (53.5)
FACIT, mean (S.D.)	35.1 (10.6)	35.5 (10.7)	34.5 (10.6)	35.3 (10.8)	34.7 (10.6)	35.4 (10.8)	37.1 (9.7)
Patient assessment of arthritis pain, mean (S.D.)	34.9 (26.1)	31.6 (25.8)	35.9 (25.6)	31.8 (24.5)	35.6 (25.7)	31.7 (24.9)	30.3 (24.2)
Patient global assessment of arthritis, mean (S.D.)	35.9 (25.8)	32.8 (25.7)	36.9 (25.5)	32.5 (25.1)	36.6 (25.6)	32.6 (25.3)	31.5 (24.3)
Physician global assessment of arthritis, mean (S.D.)	28.1 (22.9)	27.6 (22.1)	28.0 (22.9)	26.0 (21.6)	28.0 (22.9)	26.5 (21.8)	25.2 (21.8)
Monotherapy/combination therapy, *n* (%)							
Monotherapy	148 (31.2)	89 (30.5)	301 (27.9)	177 (28.6)	449 (28.9)	266 (29.2)	789 (32.2)
Combination therapy	249 (52.4)	146 (50.0)	630 (58.5)	352 (56.9)	879 (56.6)	498 (54.7)	1197 (48.9)
CVD at baseline, *n* (%)	185 (38.9)	140 (47.9)	465 (43.2)	319 (51.6)	650 (41.9)	459 (50.4)	916 (37.4)

FACIT: Functional Assessment of Chronic Illness Therapy; MTX: methotrexate.
[a] Patients who were ongoing at the time of the data cut or who had completed the LTE studies.

Table 2. Voluntary, involuntary and overall reasons for tofacitinib discontinuation

Characteristics	All tofacitinib ($N = 4967$)	Tofacitinib 5 mg BID ($n = 1535$)	Tofacitinib 10 mg BID ($n = 3432$)
Total discontinuation rate[a], *n* (%)	2518 (50.7)	792 (51.6)	1726 (50.3)
Voluntary	1552 (31.2)	475 (30.9)	1077 (31.4)
Involuntary	911 (18.3)	292 (19.0)	619 (18.0)
Patient died	55 (1.1)	25 (1.6)	30 (0.9)
Reason for voluntary discontinuations, *n* (%)			
Relation to study drug not defined	1123 (22.6)	319 (20.8)	804 (23.4)
No longer willing to participate	504 (10.1)	133 (8.7)	371 (10.8)
Other	307 (6.2)	92 (6.0)	215 (6.3)
Insufficient clinical response	179 (3.6)	63 (4.1)	116 (3.4)
Lost to follow-up	133 (2.7)	31 (2.0)	102 (3.0)
AE (study drug related)	270 (5.4)	99 (6.4)	171 (5.0)
AE (not study drug related)	159 (3.2)	57 (3.7)	102 (3.0)
Reason for involuntary discontinuations, *n* (%)			
Relation to study drug not defined	151 (3.0)	50 (3.3)	101 (2.9)
Protocol violation	127 (2.6)	38 (2.5)	89 (2.6)
Withdrawn due to pregnancy	18 (0.4)	10 (0.7)	8 (0.2)
Does not meet entrance criteria	4 (0.1)	2 (0.1)	2 (0.1)
Medication error without associated AE	1 (0.0)	0 (0.0)	1 (0.0)
Study terminated by sponsor	1 (0.0)	0 (0.0)	1 (0.0)
AE (study drug related)	545 (11.0)	174 (11.3)	371 (10.8)
AE (not study drug related)	215 (4.3)	68 (4.4)	147 (4.3)

[a] Included patients who voluntarily and involuntarily discontinued or who died.

treatment due to voluntary *vs* involuntary reasons, with competing risks accounted for.

When stratified by geographic region, patients enrolled at European sites generally stayed longer in the LTE studies, while patients enrolled at the USA/Canada sites were more likely to discontinue due to voluntary and involuntary reasons, with involuntary and voluntary discontinuation as competing risks, respectively, during the LTE studies (Fig. 2B and D).

When involuntary discontinuation was included as a competing risk for voluntary discontinuation in the multivariable Cox regression analysis, patients who stayed on combination therapy (*vs* stayed on monotherapy) or those with higher patient-assessed pain (visual analogue scale) were significantly more likely to discontinue for voluntary reasons (Fig. 3). The influence of region was particularly notable. Patients enrolled at European sites were much less likely to voluntarily discontinue treatment compared with those enrolled in the USA/Canada [HR 0.66 (95% CI 0.57, 0.78)], and those enrolled in Latin America and Asia were likewise less likely to voluntarily discontinue. Older patients and seropositive patients (RF^+/CCP^+ *vs* RF^-/CCP^-) were also significantly less likely to discontinue for voluntary reasons (Fig. 3). Univariate results are included in Supplementary Fig. S2, available at *Rheumatology Advances in Practice* online. When voluntary discontinuation was included as a competing risk for involuntary discontinuation in the multivariable Cox regression analysis, older patients, patients with diabetes, patients with CVD, seropositive patients and those who received a higher index GC dose (>10 *vs* 0 mg/day) were more likely to involuntarily discontinue (Supplementary Fig. S3B, available at *Rheumatology Advances in Practice* online). Patients enrolled in Europe were less likely to involuntarily discontinue compared with those enrolled in the USA/Canada, as were patients with a body mass index (BMI) of 25–30 kg/m^2 (*vs* >30 kg/m^2) (Supplementary Fig. S3B, available at *Rheumatology Advances in Practice* online). Univariate results are included in Supplementary Fig. S3A, available at *Rheumatology Advances in Practice* online.

In the multivariable Cox regression analysis where competing risk was not included, a few additional factors emerged. For voluntary discontinuation, these included lower BMI (<25 *vs* >30 kg/m^2), higher DAS28-4ESR and receiving tofacitinib 5 mg BID (*vs* 10 mg BID); these were associated with greater likelihood of voluntarily discontinuation of tofacitinib during the LTE studies (Supplementary Fig. S4A, available at *Rheumatology Advances in Practice* online). For involuntary discontinuation, an additional factor associated with a greater likelihood of involuntary discontinuation was a higher index GC dose (>5–10 *vs* 0 mg/day). Patients who received mixed therapy (*vs* stayed on monotherapy) or were non-smokers were less likely to involuntarily discontinue (Supplementary Fig. S4B, available at *Rheumatology Advances in Practice* online). Univariate results are included in Supplementary Figs S5 and S6, available at *Rheumatology Advances in Practice* online.

Only small numeric differences in disease activity at the time of discontinuation, measured using the last available DAS28-4ESR score, were observed between geographic regions among those patients who voluntarily or involuntarily discontinued tofacitinib. Disease activity was marginally lower for patients discontinuing for involuntary *vs*

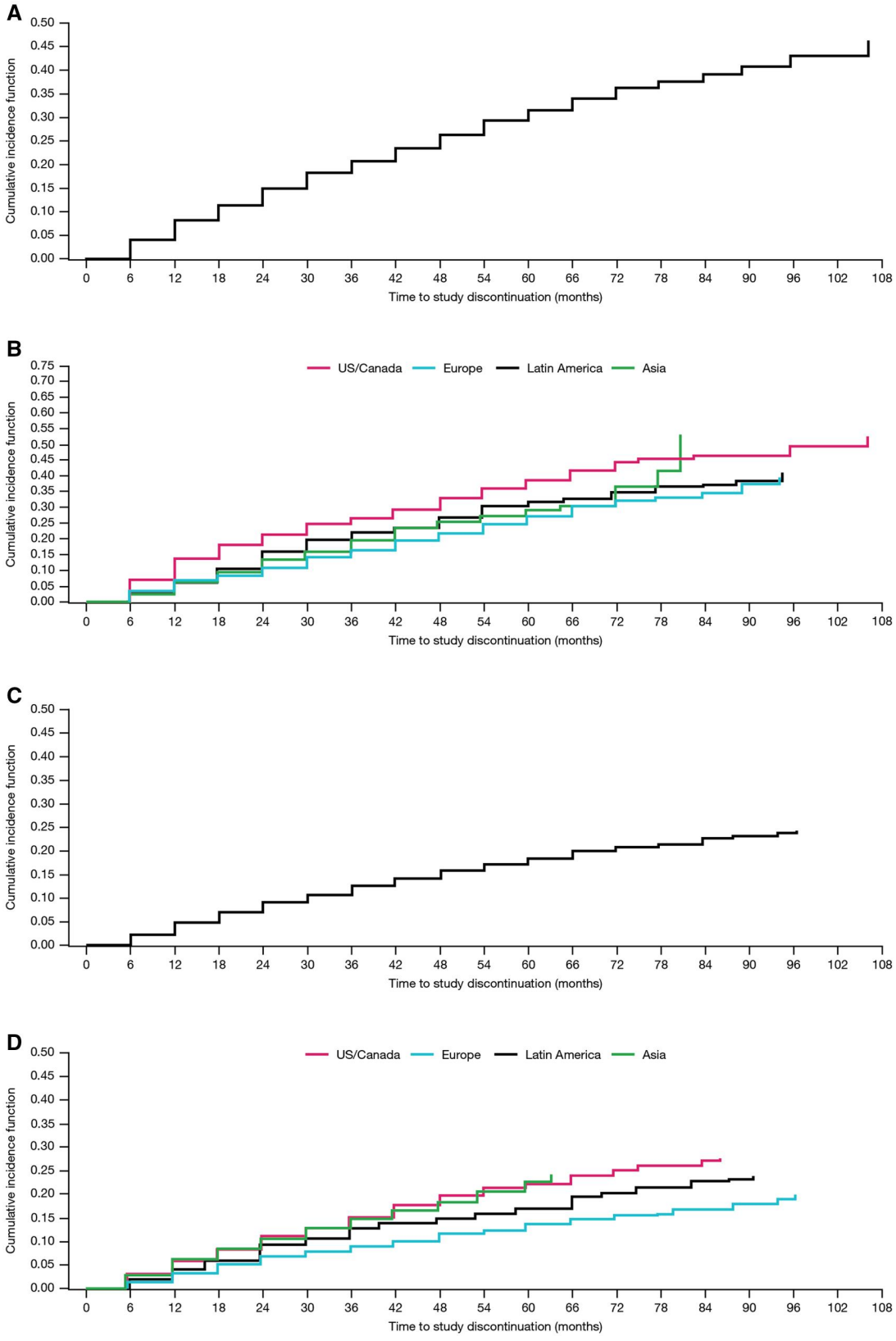

Figure 2. Time to tofacitinib discontinuation. Cumulative incidence of voluntary discontinuation with involuntary discontinuation as a competing risk and involuntary discontinuation with voluntary discontinuation as a competing risk via the Aalen–Johansen estimation. Tofacitinib discontinuation due to voluntary reasons with involuntary discontinuation as a competing risk for **(A)** all patients and **(B)** by geographic region and due to involuntary reasons with voluntary discontinuation as a competing risk for **(C)** all patients and **(D)** by geographic region. Time to discontinuation defined as the difference between the end-of-study date and the first tofacitinib dose date + 1 day. Patients missing an end-of-study case report form were censored at the cutoff date. Completers were censored at the end-of-study date

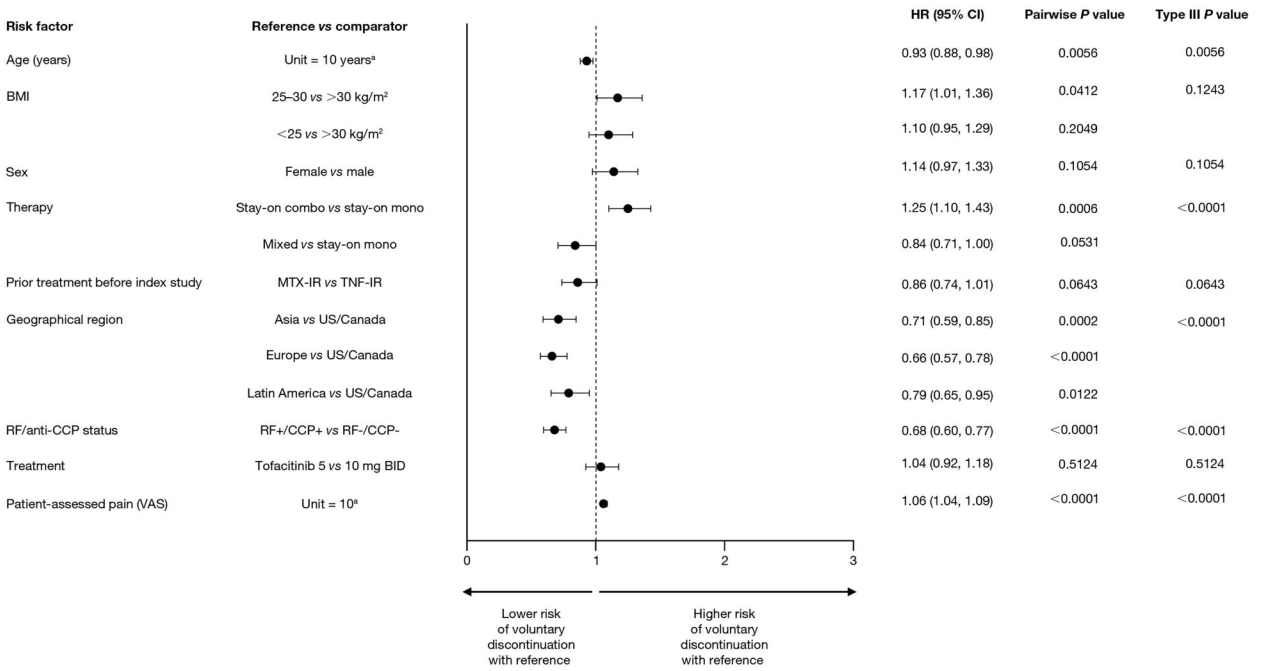

Figure 3. HRs (95% CIs) for voluntary discontinuation using involuntary discontinuation as a competing risk using multivariable Cox regression analysis. Based on the proportional subdistribution hazards model of Fine and Gray [12]. [a]ln unit = *x*, where *x* is the change in the continuous variable corresponding to which change in hazards is observed. combo: combination therapy; IR: inadequate responder; mixed: patients who adjusted combination/monotherapy during the long-term extension studies at the investigator's discretion; mono: monotherapy; MTX: methotrexate; VAS: visual analogue scale

voluntary reasons (Supplementary Table S2, available at *Rheumatology Advances in Practice* online). DAS28-4ESR was generally lower for patients completing the studies, compared with those who discontinued for any reason, and for those not enrolled in the USA/Canada (Supplementary Table S2 and Supplementary Fig. S7, available at *Rheumatology Advances in Practice* online).

Safety

Table 3 presents a summary of treatment-emergent AEs and SAEs over the course of the LTE studies for patients who discontinued for voluntary and involuntary reasons. Compared with patients who discontinued for voluntary reasons, patients who involuntarily discontinued had higher EAERs for AEs and SAEs and discontinuations due to AEs and SAEs. In patients who discontinued for involuntary reasons, EAERs were numerically higher across most outcomes for patients receiving tofacitinib 10 *vs* 5 mg BID but were generally comparable between doses for voluntary discontinuations. Of all patients receiving tofacitinib, the most common AE was upper respiratory tract infection for both those who voluntarily discontinued or involuntarily discontinued. For all patients receiving tofacitinib and when stratified by dose received, the most common SAE was osteoarthritis for those who voluntarily discontinued (EAER for all tofacitinib 0.8) and pneumonia for those who involuntarily discontinued (EAER for all tofacitinib 4.2).

Discussion

This analysis of data from two large LTE studies of tofacitinib in RA extends previous work in this area [3, 6] by examining more closely the reasons underlying treatment discontinuation, whether instigated by the patient (voluntarily) or protocol mandated (involuntarily), and the contributing factors associated with each.

In total, 49.6% of patients discontinued tofacitinib over the course of 9.5 years. For all treated patients, rates of voluntary discontinuation were higher than those of involuntary discontinuation (31.2% *vs* 18.3%, respectively). Although patient characteristics at the start of the index studies were broadly similar between discontinuation groups, demographic data suggest that patients who discontinued tofacitinib for involuntary reasons were older, had a higher comorbid disease burden, were more likely to be obese and have a history of smoking and were less likely to use combination therapy. Patient-reported pain and patient- and physician-perceived disease severity scores were slightly worse among those patients who chose to discontinue treatment than for patients who involuntarily discontinued. Furthermore, across all regions, a higher proportion of tofacitinib-treated patients discontinued due to voluntary rather than involuntary reasons. Moreover, we found strong regional differences in the rates of voluntary discontinuation, with patients enrolled in the USA and Canada more likely to voluntarily discontinue from the LTE studies. These observations persisted even after multivariable adjustment for other potentially confounding factors and when considering involuntary discontinuation as a competing risk, as described below. These findings indicate there are important potential differences between patient groups voluntarily or involuntarily discontinuing tofacitinib and may be used to inform future study design of long-term studies. However, it should be noted that differences in response rates between geographic regions have also previously been reported in patients with RA receiving placebo [13].

Our data show that most voluntary discontinuations (72.4%) were not related to AEs and pertained mostly to withdrawal of consent by the patient, insufficient clinical

Table 3. Treatment-emergent AEs and SAEs for patients who discontinued tofacitinib due to voluntary/involuntary reasons

Characteristics	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		All tofacitinib	
	Voluntary reasons (*n* = 475)	Involuntary reasons (*n* = 292)	Voluntary reasons (*n* = 1077)	Involuntary reasons (*n* = 619)	Voluntary reasons (*n* = 1552)	Involuntary reasons (*n* = 911)
Total exposure, PY	1256	744	2393	1290	3649	2034
Patients with AE, *n* (EAER)	419 (33.4)	279 (37.5)	923 (38.6)	602 (46.7)	1342 (36.8)	881 (43.3)
Discontinued due to AE, *n* (EAER)	158 (12.6)	240 (32.3)	278 (11.6)	522 (40.5)	436 (12.0)	762 (37.5)
Patients with SAE, *n* (EAER)	124 (9.9)	183 (24.6)	247 (10.3)	428 (33.2)	371 (10.2)	611 (30.0)
Discontinued due to SAE, *n* (EAER)	53 (4.2)	157 (21.1)	101 (4.2)	382 (29.6)	154 (4.2)	539 (26.5)
Most common AE[a], *n* (EAER)						
Upper respiratory tract infection	62 (4.9)	54 (7.3)	161 (6.7)	91 (7.1)	233 (6.1)	145 (7.1)
Nasopharyngitis	78 (6.2)	51 (6.9)	138 (5.8)	66 (5.1)	216 (5.9)	117 (5.8)
Pneumonia	17 (1.4)	25 (3.4)	32 (1.3)	83 (6.4)	49 (1.3)	108 (5.3)
Urinary tract infection	47 (3.7)	47 (6.3)	121 (5.1)	97 (7.5)	168 (4.6)	144 (7.1)
Bronchitis	51 (4.1)	33 (4.4)	105 (4.4)	75 (5.8)	156 (4.3)	108 (5.3)
Herpes zoster	42 (3.3)	37 (5.0)	93 (3.9)	71 (5.5)	135 (3.7)	108 (5.3)
Most common SAE[b], *n* (EAER)						
Pneumonia	1 (0.1)	19 (2.6)	2 (0.1)	66 (5.1)	3 (0.1)	85 (4.2)
Herpes zoster	1 (0.1)	12 (1.6)	3 (0.1)	14 (1.1)	4 (0.1)	26 (1.3)
Urinary tract infection	1 (0.1)	7 (0.9)	1 (0.0)	13 (1.0)	2 (0.1)	20 (1.0)
Osteoarthritis	7 (0.6)	6 (0.8)	22 (0.9)	7 (0.5)	29 (0.8)	13 (0.6)
Cellulitis	0	6 (0.8)	4 (0.2)	10 (0.8)	4 (0.1)	16 (0.8)
Diverticulitis	1 (0.08)	5 (0.7)	0	12 (0.9)	1 (0.03)	17 (0.8)
Breast cancer	0	6 (0.8)	0	11 (0.9)	0	17 (0.8)

[a] Defined as AEs with EAER ≥5.0 in the all-tofacitinib treatment group.
[b] Defined as SAEs with EAER ≥0.8 in the all-tofacitinib treatment group.

response or reasons not specified. It is conceivable that some patients opted to stop treatment with tofacitinib for reasons of satisfactory disease control and self-perceived disease remission (thus feeling they no longer required medication), as well as inadequate disease control (feeling that the medication was not working well enough). Notably, the mean DASs at which patients voluntarily or involuntarily discontinued were all in the moderate range (DAS28-4ESR 3.2–5.1) [14] across geographic regions. In all patients discontinuing tofacitinib, regardless of whether they discontinued voluntarily or involuntarily, AEs were the most common reason for discontinuation across all geographic regions. Similar rates of discontinuation were observed across tofacitinib 5 and 10 mg BID dose groups within voluntary, involuntary and overall discontinuation categories, and appear to confirm the uniformity of response to tofacitinib.

In the earlier analysis by Pope *et al.* [3], the median persistence for tofacitinib was 4.9 years (95% CI 4.7, 5.1) and estimated 2-year persistence rates were >75%. However, the definition of 'treatment discontinuation' did not differentiate between study protocol-mandated termination and study withdrawal as a result of patient choice. Here, the drug persistence estimates via the Aalen–Johansen estimation for patients receiving tofacitinib and discontinuing for voluntary or involuntary reasons, with involuntary or voluntary discontinuation as a competing risk, respectively, were presented. A higher percentage of patients discontinued tofacitinib treatment due to voluntary *vs* involuntary reasons over the course of the LTE studies when competing risk was included in the analysis.

Geographic differences were also observed in the drug persistence analysis via the Aalen–Johansen estimation. These differences may deserve further investigation given the common protocol applied, but also the possible existence of differences in baseline patient characteristics among geographic regions and site differences in treatment adjustments applied during the LTE studies.

As alluded to above, patients who were involuntary discontinued would not have had a chance to voluntarily discontinue, so we performed competing risk analyses to determine whether the likelihood of voluntary discontinuation of tofacitinib was modified by involuntary discontinuation. Our results demonstrated that age, therapy regimen (stay on combination therapy *vs* stay on monotherapy), geographic region, RF/anti-CCP status and patient-assessed pain were all significant factors for voluntary discontinuation with involuntary discontinuation as a competing risk. When compared with the results of the multivariable Cox regression analyses without competing risk, the results of the competing risk analyses appear to be more clinically meaningful, particularly in terms of geographic region. Specifically, patients enrolled in Europe were 34% less likely to discontinue voluntarily than those enrolled in the USA or Canada. Likewise, patients enrolled in Asia were 29% less likely to discontinue voluntarily and those enrolled in Latin America were 21% less likely compared with patients enrolled in the USA/Canada. Patients enrolled in Europe were also 44% less likely to discontinue involuntarily than those enrolled in the USA/Canada. As noted above, these results further support the strong regional differences in the rates of voluntary discontinuation in the tofacitinib LTE studies. For involuntary discontinuation using voluntary discontinuation as a competing risk, some differences were observed *vs* for voluntary discontinuation with involuntary discontinuation as a competing risk. Namely, for involuntary discontinuation, diabetes, BMI, CVD and higher

index GC dose were additional significant factors affecting discontinuation. Notably, in contrast with voluntary discontinuation, therapy regimen and patient-assessed pain were not significant factors affecting involuntary discontinuation.

In the previous analysis, negative RF/anti-CCP status, inadequate response to TNF inhibitors (rather than inadequate response to methotrexate) and the presence of baseline diabetes or hypertension were associated with an increased risk of treatment discontinuation [3]. Here, we showed that factors influencing treatment persistence differed according to whether the patient was voluntarily or involuntarily discontinuing tofacitinib treatment. From our analyses without competing risk, our findings suggest that lower BMI, continued use of combination therapy (*vs* continued use of monotherapy), higher DAS28-4ESR and treatment with tofacitinib 5 mg BID (*vs* 10 mg BID) may increase a patient's risk of voluntary tofacitinib discontinuation. Additional factors associated with increased risk of involuntary discontinuation, but not with voluntary discontinuation, were age (older *vs* younger), history of diabetes (yes *vs* no), history of CVD (yes *vs* no), geographic region and higher index GC dose (>10 *vs* 0 mg/day or >5–10 *vs* 0 mg/day). This may indicate that patients who involuntarily discontinued had more comorbidities and therefore were at a higher risk of having an AE/SAE than those who voluntarily discontinued. The toxicity of higher-dose steroid treatment is well documented in RA [15] and may have contributed to involuntary discontinuations due to the association of higher-dose GC and serious infections, for which withdrawal was required as per the study protocols [16].

Notably, only small numeric differences in the last available DAS28-4ESR scores were observed between geographic regions in the voluntary and involuntary discontinuation groups, with the highest disease activity observed in patients enrolled in the USA and Canada. Based on distribution by disease activity status, there was marginally better control in patients who completed rather than discontinued treatment for any reason. Mean disease activity also appeared marginally lower in those who involuntarily discontinued *vs* those who voluntarily discontinued; therefore, those who voluntarily discontinued may have been unhappy with their level of disease control and decided to stop treatment. These findings suggest that disease activity may be an influencing factor in tofacitinib discontinuation, and if a patient is doing well, they are less likely to drop out of an LTE study.

With regard to safety, in this analysis, patients who involuntarily discontinued generally had higher EAERs for AEs and SAEs and discontinuations due to AEs and SAEs than patients who discontinued voluntarily, as expected. In addition, higher EAERs were seen across most outcomes for patients receiving tofacitinib 10 *vs* 5 mg BID, irrespective of voluntary or involuntary discontinuation.

It is important to acknowledge that our variable selection was based on statistical stepwise selection criteria (*P*-value <0.15) and may not always translate to clinical significance. Some risk factors could be confounded, as the dose of tofacitinib (5 or 10 mg BID) will have had an impact on time-dependent DAS28-4ESR, which was measured during the study (post-baseline). Furthermore, the homogeneity of patient baseline characteristics, as a consequence of stringent study enrolment criteria in the index studies, may lead to less generalizability of the results from this study to a wider RA population. Finally, only the single most relevant reason for discontinuation was recorded on the case report form, which may have resulted in underestimation of all reasons contributing to, and perhaps even misclassification of, the most important reason for study withdrawal. Moreover, the analysis of competing risk was conducted as a sensitivity analysis here, which we believe to be a limitation of this analysis [17]. Furthermore, this analysis was exploratory, and this should be kept in mind when interpreting results.

In conclusion, different factors were associated with treatment discontinuation among patients voluntarily and involuntarily discontinuing tofacitinib in LTE studies. Wide variability in voluntary discontinuation (i.e. attrition) was observed in relation to the region of the world in which patients were recruited. These observations emphasize the importance of more accurately capturing reasons for treatment discontinuation in the clinical study setting as well as in real-world data acquisition. These findings suggest that treatment persistence in RA clinical studies may be predictable, at least at a group level, which may be reflected in clinical practice. Applying these results to clinical study design may help us to better plan for and potentially mitigate attrition in future clinical studies in RA.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Authors' contributions

J.R.C., L.W. and V.T. were involved in the conception or design of the study. J.W. and L.W. were involved in the acquisition of data. J.R.C., J.W., L.W., K.R. and V.T. were involved in the analysis of data. J.R.C., J.W., S.W.T., K.C., L.W., K.R. and V.T. were involved in the interpretation of data. All authors drafted or substantially revised this work and approved the manuscript for submission.

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