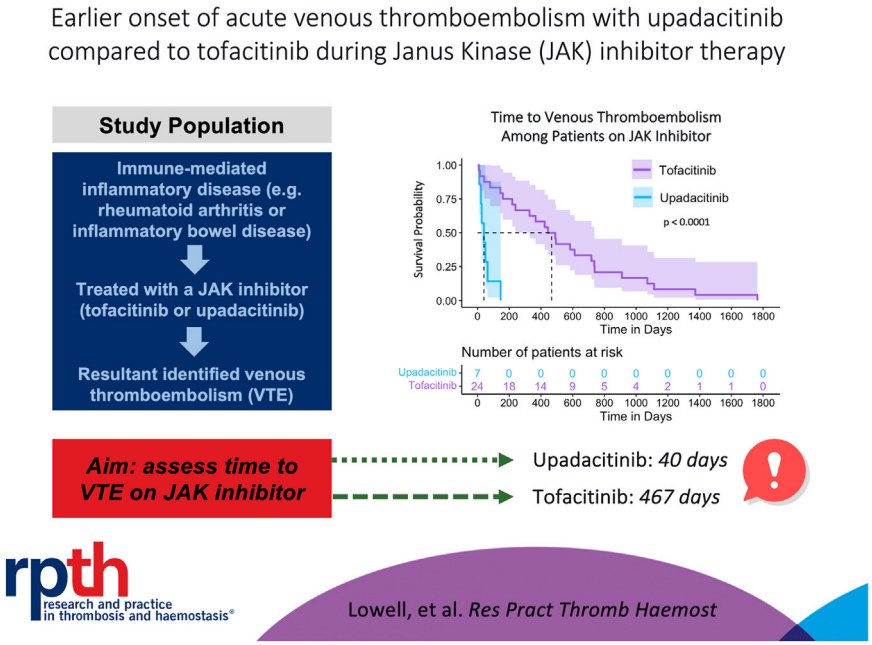
Received: 5 April 2024 | Revised: 28 April 2024 | Accepted: 9 May 2024

https://doi.org/10.1016/j.rpth.2024.102440

RESEARCH LETTER

Earlier onset of acute venous thromboembolism with upadacitinib compared with tofacitinib during Janus kinase inhibitor therapy



The risk of venous thromboembolism (VTE) is increased in patients with immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis and inflammatory bowel disease (IBD). Tofacitinib and upadacitinib are Janus kinase inhibitors (JAKis) that have emerged as effective therapies for these patients. However, their utilization is currently hampered by a warning for increased VTE risk, with studies to date predominantly performed in patients with rheumatoid or psoriatic arthritis. There is limited data on the time to VTE occurrence in patients after initiating a JAKi. Despite a relatively rapid onset of action of 2 to 12 weeks, patients using a JAKi for a short duration are often excluded from safety profiles and clinical trials. As such, it remains unclear if this early trial period in which JAKi efficacy is typically assessed is safe with regard to VTE timing. Our goal was not to assess VTE risk with JAKi but rather to observe the timing of VTE events that occurred among patients receiving JAKi.

We retrospectively evaluated a cohort of adult patients (≥18 years old) within a large hospital network, including subsidiary outpatient clinical encounters, between the initial United States Food and Drug Administration approval of tofacitinib (November 2012) and June 2023 to identify those that developed a VTE while on JAKi therapy (tofacitinib or upadacitinib). The search strategy identified patients with a prescription for a JAKi and either an International Statistical Classification of Diseases and Related Health Problems-10 coded VTE event or overlapping prescription of anticoagulation (apixaban, rivaroxaban, or warfarin within 1 year of JAKi prescription). Patient charts were manually reviewed for adjudication that the VTE event was new, unprovoked, and occurred during JAKi use rather than before or after. "Unprovoked" in this context was used to describe VTE events that lacked a discernable precipitating etiology outside of JAKi use or risk from underlying IMID or cardiovascular disease. Statistical comparisons were performed with

Mann–Whitney U-test, log-rank analysis, or Fisher's exact test as appropriate.

A total of 152 patients had any documented prescription for JAKi with either an International Statistical Classification of Diseases and Related Health Problems-10 coded VTE or prescription for anticoagulation, representing 288.9 patient-years (median, 1.37 y/patient) on JAKi therapy. From this population, we identified 36 patients who experienced a new VTE while on JAKi therapy (tofacitinib = 29 events, upadacitinib = 7 events). Patients with an identifiably provoked VTE (n = 5) attributable to causes outside of JAKi use, including recent surgery or trauma and active cancer on chemotherapy treatment, were removed from downstream analysis. Comparison of patients with VTE on tofacitinib with those on upadacitinib revealed no statistical differences in baseline characteristics, including sex (gender assigned at birth), body mass index, race, smoking status, disease treated by JAKi, or comorbidities including Charlson comorbidities index (Table). The age of patients with VTE during JAKi use trended higher for patients receiving tofacitinib (72.5 years; IQR, 64.3-80.3) compared with patients receiving upadacitinib (56 years; IQR, 55.5-71; P = .103). Among the patients with a new VTE during JAKi therapy, nearly all were being treated for inflammatory arthritis (n = 30; 96.8%), and all were receiving a daily JAKi dosage consistent with a maintenance regimen at time of VTE (Table).

The median time to VTE event was 328 days (IQR, 56-665; Figure 1A). There was a significant difference in time to VTE when comparing JAKi therapies, with a median of 467 days (IQR, 204-737) for tofacitinib and 40 days (IQR, 23.5-56) for upadacitinib by log-rank testing (P < .0001; Figure 1B). Further evaluation showed an additional 4 VTEs occurred within 90 days of stopping JAKi, with a median time to VTE after stopping JAKi of 19 days (range, 7-50) for the 3 patients treated with tofacitinib and 44 days for the 1 upadacitinib patient. Reasons for stopping JAKi included 2 cases of tuberculosis infection and 1 instance each of recurrent infections and IMID symptoms refractory to JAKi. Evaluation of smoking status found a nonsignificant trend toward earlier time to VTE formation among former and active smokers compared with never-smokers by log-rank analysis (P = .30).

The overall risk of thrombosis with JAKi approximates 0.2% to 0.5% per year. However, the majority of these studies have been carried out in rheumatoid or psoriatic arthritis patients. Although certain studies found no specific pattern regarding time to VTE onset with tofacitinib or upadacitinib use [1–6], other larger studies of tofacitinib or upadacitinib reported a time to VTE event primarily within a shorter timeframe of <120 days in addition to an overall distribution with positive skew [7–10]. If VTE events were to primarily cluster within the 2 to 12-week period of efficacy assessment, then initiating a JAKi for remission induction or to trial efficacy in patients that require additional disease control could lead to an avoidable consequence of VTE before demonstrating benefit. Our retrospective study revealed a difference in the time to VTE event between tofacitinib and upadacitinib. Specifically, the time to VTE on tofacitinib (328 days) was beyond the typical trial period, while the time to VTE on upadacitinib (40 days) was within the trial period. There were also 4 VTE events that occurred within 90 days of stopping JAKi, which was stopped in 3 of 4 cases due to severe infection and once due to refractory disease. Though these medications possess a short activity half-life compared with biologic alternative therapies such as infliximab, this result may suggest clinicians should maintain vigilance for VTE formation in this period, even if a JAKi is stopped for reasons other than nonresponse. Furthermore, we found a nonsignificant trend toward increased age for patients with VTE during tofacitinib use compared with those receiving upadacitinib, potentially highlighting age as a discriminatory factor when assessing VTE risk for these JAKi medications.

The limitations of our study include a small study cohort size that underpowers subgroup analyses and retrospective nature leading to selection bias. A significant limitation relates to the unknown etiology of VTE events in the patients observed. While JAKi may have been the cause for some, it is possible that for others, the cause of VTE may have been the patient's underlying inflammatory disease or cardiovascular risk factors, if present. Also, it is worth noting that the choice of which JAKi used was not directed by any institutional protocol. As such, disease activity may have played a role in medication choice, with the lack of documented disease activity scores prohibiting this analysis. Additionally, given the more recent approval of upadacitinib compared with tofacitinib, the combination of bias in selection of patients for treatment by clinicians and fewer overall patient-years of exposure for analysis may amplify the signal for rarer adverse effects such as VTEs. However, the number of patients with a VTE on JAKi therapy was ultimately comparable with other much larger randomized clinical trials or real-world studies. Further, our patient search strategy prevented extrapolation of the findings to make conclusions regarding the propensity for VTE on JAKi therapy when comparing IMIDs such as rheumatoid arthritis and IBD. Lastly, the majority of patients within this study were being treated with a JAKi for rheumatoid or psoriatic arthritis, limiting generalizability of the findings to other IMIDs, such as ulcerative colitis, for which there was only 1 patient present within the total VTE cohort.

In summary, our results are not meant to suggest an increased VTE risk for upadacitinib vs tofacitinib or with JAKi more generally, but rather that upadacitinib may incur a thrombosis risk earlier in treatment course compared with tofacitinib, notably overlapping with the typical 2 to 12-week period of JAKi benefit assessment. It has yet to be seen whether these timeframes of VTE occurrence found in the present study apply similarly to patients with IBD vs other IMIDs. It will also be important to understand if this earlier time to VTE is specific to upadacitinib. These findings require replication to validate the respective time on JAKi until VTE event. Our findings do not specifically guide whether to choose therapy with a JAKi or not, but may impact the choice of which JAKi to utilize as part of a model of shared decision-making between doctors and patients when weighing the benefits vs risks of treatment.

FUNDING

None.

TABLE Characteristics of patients with venous thromboembolism on Janus kinase inhibitor.

Characteristic	VTE on JAKi	VTE on tofacitinib	VTE on upadacitinib	*P* value
Patients, *N*	31	24	7	
Age, y, median (IQR)	70 (59-80)	72.5 (64.3-80.3)	56 (55.5-71)	.10[a]
BMI, median (IQR)	31 (28.1-36.5)	31 (27.6-35.1)	30.8 (28.2-39.1)	.99[a]
Sex, *n*				.56
Male	5	3	2	
Female	26	21	5	
Race, *n*				.75
White/Hispanic	23	18	5	
Black	5	4	1	
Unknown	2	1	1	
Smoking, *n*				1
Never	16	12	4	
Ever	15	12	3	
Comorbidities, *n* (%)				.56
Type 2 diabetes	7 (22.6)	5 (20.8)	2 (28.6)	
Congestive heart failure	2 (6.5)	2 (8.3)	0	
Chronic obstructive lung disease	6 (19.4)	5 (20.8)	1 (14.3)	
Chronic kidney disease	1 (3.2)	0	1 (14.3)	
Liver cirrhosis	0	0	0	
Hypertension	20 (64.5)	16 (66.7)	4 (57.1)	
Dyslipidemia	17 (54.8)	14 (58.3)	3 (42.9)	
Charlson comorbidity index, median (IQR)	5 (3-6)	5 (3-6.25)	4 (2-5)	.39[a]
Disease treated by JAKi, *n* (%)				.55
Ulcerative colitis	1 (3.2)	1 (4.2)	0	
Rheumatoid arthritis	28 (90.3)	22 (91.7)	6 (85.7)	
Psoriatic arthritis	2 (6.5)	1 (4.2)	1 (14.3)	
JAKi dosage, median (mg)	–	11	15	
Time on JAKi, total patient-y[c]	80.1	69.2	10.9	
Time on JAKi, median (IQR)[c]	2.0 (0.62-4.28)	1.32 (0.47-3.04)	0.67 (0.21-1.62)	
Time to VTE, median (IQR)	328 (56-665)	467 (204-737)	40 (23.5-56)	<.001[b]
VTEs <90 d after stopping JAKi	4	3	1	
Time to VTE after stopping JAKi, median (range)	31.5 (7-50)	19 (7-50)	44	

P values reflect Fisher's exact test comparing tofacitinib and upadacitinib.

BMI, body mass index; JAKi, Janus kinase inhibitor; VTE, venous thromboembolism.

[a]Mann–Whitney U-test comparing tofacitinib and upadacitinib.

[b]Log-rank analysis comparing tofacitinib and upadacitinib.

[c]Values derived from parent population, including those without VTE on JAKi.

AUTHOR CONTRIBUTIONS

J.A.L. and K.S. conceptualized and planned the study. J.A.L. and G.S. collected the data. J.A.L. and K.S. interpreted the data and conducted analyses. J.A.L. drafted the manuscript and prepared the figures. K.S. provided expert guidance and advice. J.A.L., G.S., and K.S. edited and revised the manuscript. All authors have approved the submission of the manuscript's final draft.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

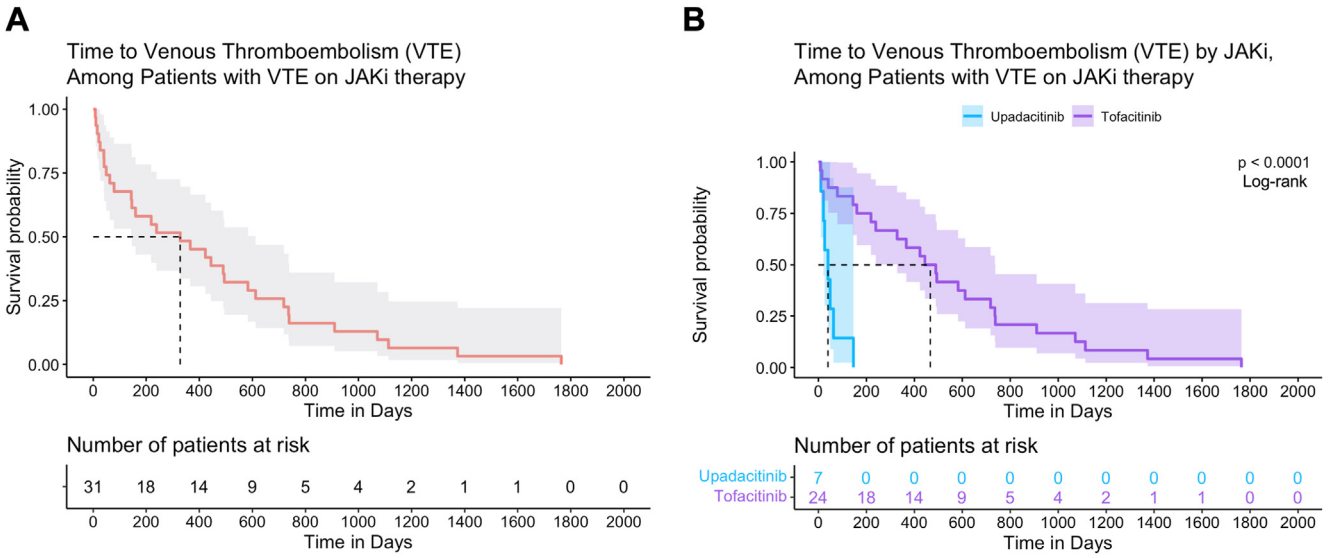


FIGURE 1 Survival curve plots showing time from initiation of Janus kinase inhibitor (JAKi) to time of venous thromboembolism (VTE) event in days. Remaining number of patients at risk is displayed below each plot. Median survival is demonstrated by dotted line intersecting 50% survival probability and median time to VTE for the patient group. The shaded area shows 95% CI. (A) For all patients with VTE during JAKi therapy, median time to VTE was 328 days (IQR, 56-665). (B) Patients with VTE during JAKi are separated by JAKi type. Median time to VTE for upadacitinib (blue) was 40 days (IQR, 23.5-56), and for tofacitinib (purple) was 467 days (IQR, 204-737; log-rank $P < .0001$).

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Handling Editor: Kristen Sanfilippo

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