Lessons from tofacitinib in patients with cardiovascular risk factors: increased pulmonary embolism or isolated (thrombotic) pulmonary occlusion rates?

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Recent treatments of patients with rheumatoid arthritis (RA) and other immune-mediated inflammatory diseases (IMIDs) have substantially changed patients' outcome and advanced risk management, that is, risks related to the disease and certain drugs.[1] In this regard, rheumatologists became well aware of the overall increased risks for arterial complications (arterial thrombotic events (ATE), acute myocardial infarction and stroke), infections and venous thromboembolic events (VTE) by the underlying diseases. In addition, certain disease-modifying antirheumatic drugs (DMARDs) have been linked to increased risks, that is, specific infections (TNF-i with tuberculosis and Jak inhibitor (Jak-i) with herpes zoster reactivation, and anti-CD20 with progressive multifocal leukencephalopathy (PML)) or other complications (anti-interleukin-6 receptor (IL-6R) blockade with lower intestinal perforations, anti-interleukin-17 with inflammatory bowel disease (re)exacerbation). Precautions to mitigate these risks have been introduced in clinical practice.

The introduction of Jak-i not only resulted in improved therapeutic responses but also regained particular interest into VTEs, which have been included as adverse events/warnings in their labels recently. Compared with expected VTE rates ranging between 0.3 and 0.8/100 patients years (PY) for RA under different conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biological disease-modifying antirheumatic drugs (bDMARDs) (a twofold increase compared with controls),[2 3] 4 mg baricitinib had an increased VTE rate of 1.3/100 PY but none in the 2 mg dose and placebo groups during the placebo-controlled period of 24 weeks.[4] This observation influenced the approval of 2 mg but not 4 mg baricitinib by the Food and Drug Administration, while long-term extension data show VTE rates of 0.3/100 PY for both dosages.[4] Important mechanistic and clinical questions about the role of Jak-i and VTEs remain to be delineated, including studies assessing the actual VTE risk in RA outside registration trials.

In *ARD*, the study by Mease *et al*[5] reports post hoc data of patients with cardiovascular risk (50 years or older with at least one cardiovascular risk factor) from the tofacitinib development in the context of data submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency and other real-world data. PRAC reviewed an ongoing post-authorisation study (A3921133) in patients with RA, psoriatic arthritis (PsA) and psoriasis (PsO) with cardiovascular risk factors treated with 5 and 10 mg tofacitinib or an TNF-i, and reported increased all-cause mortality, sixfold increased PE risk with 10 mg and threefold with 5 mg (not significant) versus TNF-i. The deep vein thrombosis (DVT) risk was numerically but not statistically significantly increased by both tofacitinib doses versus TNF-i. As a result, the use of tofacitinib has been limited by regulators.

The current independent analysis[5] assessed patients with RA, PsO and PsA enriched for ATE and VTE risk factors from the tofacitinib trials. Although not powered for safety, VTE incidence rates (IRs) were higher for patients with risk factors, especially PE rates

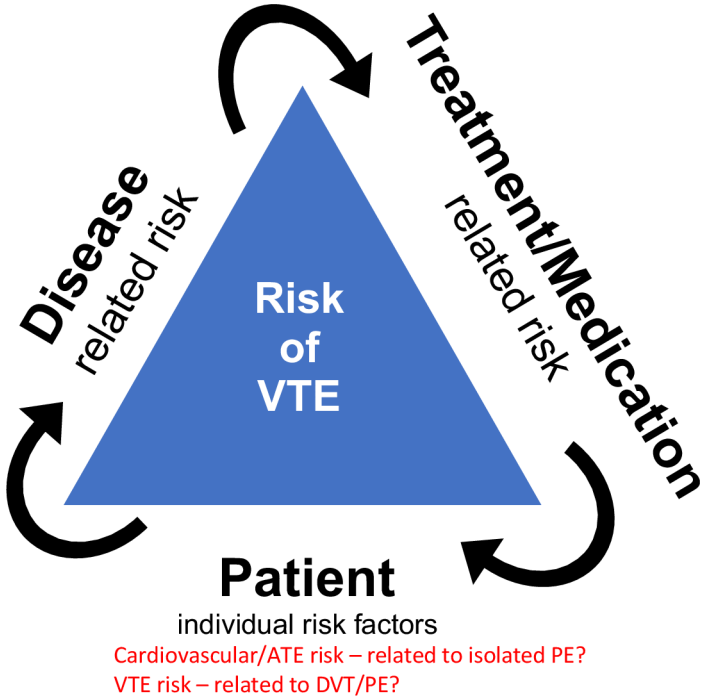

Figure 1 Triad of VTE risk assessment requires consideration of individual patient factors, underlying disease (including potential disease activity) and risks related to medication/treatment. With regard to patient risks, the study by Mease *et al*[5] reports that elevated cardiovascular (ATE) risks may contribute disproportionally to increased PE rates under 10 mg tofacitinib dose. This might indicate a potential segregation from conventional thrombophilic factors. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolic event.

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Table 1 Comparison of reported IRs of DVT and PE and the ratio of IR DVT/IR PE

	IRs	DVT	PE	IR DVT:IR PE
Tofacitinib				
RA all tofacitinib cohort	5 mg constant	0.11	0.06	1.83
	10 mg constant	0.13	0.15	0.87
RA CV risk+	5 mg	0.34	0.25	1.36
	10 mg	0.17	0.24	0.71
RA VTE risk+	5 mg	0.25	0.2	1.25
	10 mg	0.18	0.17	1.06
ENTRACTE	Etanercept	0.3	0.2	1.50
	Tocilizumab	0.2	0.06	3.33
A3921133	5 mg	0.3	0.27	1.11
	10 mg	0.38	0.54	0.70
	TNF-i	0.18	0.09	2.00
PsO all tofacitinib cohort	5 mg average	0.06	0.13	0.46
	10 mg average	0.06	0.09	0.67
PsA all tofacitinib cohort	5 mg average	0	0.08	0.00
	10 mg average	0.13	0	ND
Ulcerative colitis	5 mg predominant	0.00	0.00	ND
	10 mg predominant	0.05	0.21	0.24
Trial data (patients not enriched for ATE/VTE risk factors)				
Baricitinib[4]				
Extended data set	2 mg	0.6	0.2	3.00
	4 mg	0.3	0.3	1.00
Upadacitinib[23] (concurrent DVT/PE)				
	Pooled PBO (0)	0	0,4	0.00
	MTX (0.3)	0.3	0.5	0.60
	Adalimumab (0))	0.2	0.9	0.22
	15 mg (0.2)	0.3	0.5	0.60
	30 mg (<0.1)	0.2	0.1	2.00

Data from Mease *et al*[5] and Sandborn *et al*[24] for the ulcerative colitis programme. Available data from long-term extension studies of baricitinib[5] and the upadacitinib programme[23] among patients not enriched for risk factors are shown for comparison.
CV, cardiovascular; DVT, deep vein thrombosis; IR, incidence rate; PBO, placebo; PE, pulmonary embolism; RA, rheumatoid arthritis; VTE, venous thromboembolic event.

in patients receiving 10 mg tofacitinib two times per day. Thus, the findings are largely consistent with the interim analysis of A3921133, including the notable difference that TNF-i did not show an increase of VTEs.

INCREASED THROMBOEMBOLIC RISKS IN RA BUT UNCERTAINTIES RELATED TO RA DISEASE ACTIVITY AND DRUG SAFETY

Typical VTEs comprise DVT and/or pulmonary embolism (PE) with an overall IR for the first event ranging from 0.1 to 0.2 per 100 PY[2 3 6] in the general population. Both venous complications have been taken as an entity related to persistent and/or transient thrombophilic factors. In contrast to potentially fatal PE, DVT is considered largely preventable by prophylactic measures. PE survival after 3 months has been reported as low as 62.8% compared with 91.9% after isolated DVT,[7] along with a 30-day mortality rate of 9.7% for PE vs 4.6% for DVT.[8] Cardiovascular (ATE) and thrombophilic (VTE) risk profiles are very distinct and largely do not overlap with the exception of age, body mass index (BMI) and use of certain drugs (ie, combined oral contraceptives). Certain antirheumatic drugs, such as glucocorticoids (adjusted IR 2.31),[9] non-steroidal anti-inflammatory drugs (NSAIDs) (pooled risk ratio 1.80) and COX-2 selective inhibitors (pooled risk ratio 1.99),[10] increase VTE in addition to ATE risks. There are conflicting data among patients who started bDMARD therapy with increased VTEs excluding methotrexate (MTX)[11] or csDMARDs,[12] no changes of VTE rates on switch to TNFi[13] or reduced VTE rates after beginning of TNFi.[14] Among patients with RA under long-standing TNF-i, VTE rates of 0.37/100 PY vs 0.39 under csDMARDs have been captured by the British Society Biologic Registry (BSBR) registry.[13]

Although a potential relation between VTE rates and RA disease activity remains to be fully delineated, a recent study from Sweden[15] provided evidence that VTE rates are significantly related to disease activity with an adjusted RR of 1.99 with high RA activity, 1.45 with moderate RA activity and 1.11 with low RA activity compared with remission.

Questions emerged whether increased VTEs seen in certain trials with Jak-i can be attributed to the treatment, the disease, including disease activity, and/or individual patient risk factors (figure 1). Since the actual VTE rates were low during the development of certain Jak-i, it became difficult to identify a potential risk for individual drugs.

A meta-analysis assessing multiple Jak-i (tofacitinib, baricitinib, upadacitinib, peficitinib, decernotinib or filgotinib) versus placebo found no VTE increase for any compound versus placebo (OR for PE 0.91, p=0.87; OR for DVT 1.18, p=0.79).[16] As this study included data from 26 randomised controlled trials powered for efficacy, less patients carrying increased risks have been analysed, and the conclusion is limited to patients with RA eligible for trials. Notably, another Jak-i, ruxolitinib, approved for myeloproliferative disorders has been linked to reduced VTE rates.[17] A resulting burning question is whether there are increased VTEs as a class effect or if the different Jak-i carries distinct VTE risks, possibly related to their pharmacodynamics. This has not been conclusively delineated, especially for the majority of our patients with vascular risk factors.

The comprehensive safety assessment of two doses of tofacitinib compared with TNF-i now provides evidence for increased VTE, especially PE rates[5] in patients with increased risks when treated with 10 mg tofacitinib. In the absence of data, no firm conclusion about any other Jak-i in patients with ATE/VTE risk factors can be drawn.

THROMBOEMBOLIC PE VERSUS ISOLATED (THROMBOTIC) PE?

Another question arising from the study[5] is whether the increased PE especially under higher dosed tofacitinib occurred as isolated (thrombotic) or conventional PE related to DVT. Disproportional increase of PEs versus DVT and a stronger association with cardiovascular (ATE) than VTE risk in these patients suggest that there may be different types of pulmonary artery occlusions.

Conventional PE occurs as a complication of a prior or coexisting DVT based on a dislodged thrombus. Recently, a prevalence between 8.8%[18] and 45.4%[19] of concomitant DVT with PE has been reported. Even with best imaging techniques, occurrence rates of PE are less frequent than DVT (≤50%). Thus, the overall IRs of DVT and PE would be expected to occur around a 2:1 ratio (DVT/PE 2.0). Although there is lack of data among general RA and other IMIDs, this ratio changed under the two tofacitinib dosages (table 1) with increased PE rates. Of interest, the ratio is 2.0 under TNF-i in study A3921133.

For comparison but with several limitations, reported IRs by studies using baricitinib and upadacitinib from clinical studies in RA not enriched for risk factors show differences in the balance of DVT and PE occurrences. Predominant DVTs under baricitinib and almost consistent higher PE rates in all subgroups of the upadacitinib studies are remarkable. In the latter, more PEs than DVTs, including the separate collection of concomitant DVT/PE (table 1), have been reported throughout, including patients in the placebo, adalimumab and MTX arms, and pose the question about the actual DVT:PE ratio in RA.

PE in the absence of a DVT (isolated pulmonary embolism (i-PE)) became the focus of recent research which identified a distinct clinical and risk profile for i-PE among 3573 patients of the START2 registry.[6] Importantly, 20% fulfilled the criteria of i-PE without DVTs in the general population. Multivariate analysis revealed that older age (>75 years), female sex, heart failure or cancer, and the absence of thrombophilic alterations are risk factors. Among patients with i-PE, anticoagulation was significantly more often continued. The investigators suggested that i-PE versus DVT/PE appear to be clinically and pathogenetically different conditions.

As study A3921133 and the post hoc data of tofacitinib[5] show a preferential increase of PE compared with DVTs between the 5 and 10 mg groups (table 1), do we see increased i-PE, which may also explain the link to ATE risk factors? Although assignment of embolic versus thrombotic origin is challenging, increased i-PE would suggest that the safety signal of tofacitinib impacts distinctly on pulmonary arteries compared with conventional DVT/PE. Interestingly, VTE risk factor profiling of baricitinib reported age, BMI of >30, use of COX-2 selective NSAIDs at baseline and prior DVT/PE.[20] Except for the latter, all others are shared ATE and VTE risk factors.

SCIENTIFIC AND MEDICAL CHALLENGES

Inflammation and coagulation are closely interacting and result in higher procoagulatory activity during immune activation, consistent with the concept of thromboinflammation.[21] It is timely to consider inflammatory rheumatic diseases as persistent risk factors for provoked VTEs (as defined by the International Society on Thrombosis and Haemostasis (ISTH)) since they meet 'ongoing non-malignant condition associated with at least twofold VTE risk…, that is, inflammatory bowel disease'.[22]

In addition to increased ATE and VTE risks in RA and other IMIDs, certain anti-inflammatory agents (glucocorticoids, NSAIDs, cyclo-oxygenase-2 inhibitors and Jak-I) are associated with enhanced VTE and ATE side effects, while other compounds (TNF-i and IL-6R antagonists) do not. The study by Mease *et al*[5] substantially advanced knowledge about risks under different dosages of tofacitinib versus TNF-i; however, additional mechanistic and epidemiological studies are needed about drug-related risks and occurrences of DVT, DVT/PE and i-PE, not only for Jak-i. If patients can be better stratified according to vascular risks, it would not only guide therapeutic decisions based on safety considerations of DMARDs but also substantiate appropriate primary (and possibly secondary) prophylaxis.

Handling editor Josef S Smolen

Contributors TD searched relevant literature related to the editorial, developed the first draft and subsequently edited the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests TD has received support for clinical studies by AbbVie, Boston Pharmaceuticals, Eli Lilly, Janssen, Novartis, Roche, Sanofi, Pfizer and UCB, and honoraria for scientific advice by AbbVie, BMS/Celgene, Celtrion, Boston Pharmaceuticals, Eli Lilly, Janssen, Novartis, Roche, Samsung/Bioepis, Sanofi, Pfizer and UCB.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

To cite Dörner T. *Ann Rheum Dis* 2020;**79**:1389–1392.

Received 27 August 2020
Revised 7 September 2020
Accepted 8 September 2020

Published Online First 22 September 2020

Linked

► http://dx.doi.org/10.1136/annrheumdis-2019-216761

Ann Rheum Dis 2020;**79**:1389–1392.
doi:10.1136/annrheumdis-2020-218915

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