Thromboembolism with JAK Inhibitors for Rheumatoid Arthritis: How Real is the Risk?

Scott IC[1,2], Hider SL[1,2], Scott DL[3]

Affiliations

1. Research Institute for Primary Care & Health Sciences, Primary Care Sciences, Keele University, Staffordshire, UK.

2. Haywood Academic Rheumatology Centre, Haywood Hospital, High Lane, Burslem, Staffordshire, UK.

3. Academic Rheumatology, King's College Hospital, London, UK.

Corresponding Author: Prof DL Scott, email: d.scott1@nhs.net.

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ABSTRACT

Two different Janus Kinase (JAK) inhibitors – baricitinib and tofacitinib – are effective and licensed in active rheumatoid arthritis (RA). There have been recent concerns about potential thromboembolic risks with these drugs.

Concerns about baricitinib focus on clinical trial findings. Using all publically available data we estimate thromboembolic risks are approximately 5 events per 1,000 patient years with 4mg baricitinib daily. Concerns about tofacitinib have been raised by analyses of the Federal Drug Administration Adverse Event Reporting System (FAERs). These show some evidence of increased risks of pulmonary thrombosis, though not pulmonary embolism or venous thrombosis.

Many observational studies show thromboembolic events are increased in RA. In RA patients, there are between 3 to 8 thromboembolic events per 1,000 patient years compared with 1 to 4 events per 1,000 patient years in the general population and non-RA controls. Disease-modifying anti-rheumatic drugs and biologic treatments seem to not increase the risk of thromboembolic events, but corticosteroids may do so.

In the short-term, full details of thromboembolic events in trials of JAK inhibitors need to be published. As the numbers of thromboembolic events will be small and patients enrolled in trials are not representative of all RA patients who may receive JAK inhibitors, this information is unlikely to provide definitive answers. Consequently, in the longer-term large observational studies are needed to accurately quantify thromboembolic risks attributable to JAK inhibitors and other drugs used to treat RA, and differentiate these from risks attributable to RA itself and its comorbidities.

Janus Kinase (JAK) Inhibitors In Rheumatoid Arthritis

Two Janus Kinase (JAK) inhibitors are currently used to treat patients with active rheumatoid arthritis (RA). These comprise Bariticinib, which is approved in Europe, Japan and some other countries, and Tofacitinib, which is also approved in the United States. JAK inhibitors are considered potentially important innovations, as they represent rapidly-acting, oral treatments, which are effective in RA and other inflammatory diseases [1,2]. Tofacitinib and baricitinib are likely to be the first in a range of different JAK inhibitors, which are at various stages of their development [3].

Baricitinib And Thromboembolism

In August 2017, the Summary of Product Characteristics (SPCs) for baricitinib was revised to include a warning that deep venous thrombosis and pulmonary embolism have been reported in patients receiving baricitinib. The SPC recommended it should be used with caution in patients with risk factors for deep venous thrombosis and pulmonary embolus, such as older age, obesity, a medical history of these disorders, recent surgery or immobilisation.

Our review places this potential risk into clinical context. Firstly, we have reviewed available evidence about thromboembolic events with baricitinib. Secondly, we have assessed whether there are any thromboembolic risks with other JAK inhibitors. Thirdly we have outlined the relationship between thromboembolism and RA and other medications. Finally, we have considered the challenges assessing unexpected adverse events with new RA treatments.

Overall Risks and Benefits of JAK Inhibitors in Rheumatoid Arthritis

The potential thromboembolic risks with baricitinib need to be considered in relation to its overall efficacy and toxicity in RA. There have been seven Phase 2 and Phase 3 trials in

patients with active RA. A Bayesian network meta-analysis [4] evaluated efficacy in the 3,461 patients enrolled to these trials. Significantly more patients achieved the primary outcome - American College of Rheumatology 20 (ACR20) response rates – with baricitinib 4 mg combined with methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs) than controls. The odds ratio (OR) for achieving an ACR20 was 3.13 (95% CI 2.32-4.33), which is clinically important. Non-systematic reviews are equally supportive about its efficacy in active RA [5,6].

Data about baricitinib safety is also encouraging. The Bayesian systematic review reported that the rates of treatment-emergent adverse events were similar between baricitinib and controls [4]. Its relative safety has been confirmed in non-systematic reviews [5,6], an extension study of one of the main trials [7], and an integrated analysis of all trials [8].

One other JAK inhibitor is licensed for treating active RA, tofacitinib, which has been approved more widely including North America. There is similar strong clinical trial evidence showing it is effective with acceptable safety; these have been collated in systematic and non-systematic reviews [9-12]. Although no head-to-head trials directly compare baricitinib with tofacitinib the drugs appear broadly comparable in efficacy and toxicity. There is one other licensed JAK inhibitor – ruxolitinib – used in myelofibrosis and polycythaemia rubra vera but not in RA.

An overview of adverse events with JAK inhibitors in RA [13] highlighted risks of serious and opportunistic infections, particularly herpes zoster. However, neither this review, nor the various reports and reviews of JAK inhibitors in RA have addressed thromboembolic risks.

Current Evidence About Baricitinib And Thromboembolism

The detailed information about efficacy and overall toxicity contrasts with limited data about possible thromboembolic risks within the public domain. Publications describing the phase 2 and phase 3 trials contain some information. Six trials have been published in full [14-19]; the first trial published only as a meeting abstract contained few details about adverse events [20]. Thromboembolic events, deaths and serious adverse events in these six trials are summarised in Table 1. Three thromboembolic events were reported in the six trials: one pulmonary embolus resulted in the death of a control patient; one patient with a pulmonary embolus and another with thrombophlebitis were receiving 4mg baricitinib and neither event was fatal. Similar data is provided by the Assessment Report from the European Medicines Agency [21].

Finally, the pharmaceutical companies manufacturing baricitinib have provided a briefing document outlining the thromboembolic risks with baricitinib [22]. This document notes that seven phase 2 and phase 3 trials have been completed, with thromboembolic events occurring in five patients receiving baricitinib during the control period of two of the trials. It also states that “although an imbalance was observed during the placebo controlled period of the RA clinical trials, the rate of these events in the overall baricitinib clinical program was consistent with that seen among the general population of treated RA patients”.

There is insufficient clarity in the publically available data to reach a definitive conclusion about the thromboembolic risks with baricitinib in RA. However, it is possible to provide an estimate of its potential magnitude. The manufacturers have stated 5 patients had a thromboembolic event whilst receiving 4mg baricitinib in the randomised phase of the trials. Over 1,300 patients were randomised to this treatment but not all received 12-months of

therapy; there are about 1,000 patient years follow-up at this dosage. Consequently, the risks of developing thromboembolism with 4mg baricitinib in patients with active RA appears to be in the region of 5 cases per 1,000 patient years. In controls, there is only definite evidence of one patient with thromboembolism. The numbers of controls in these trials is similar giving a rate in the region of 1 case per 1,000 patient years, which is below that reported in RA cohorts. The small numbers of patients with thromboembolism means this level of difference between groups will not reach statistical significance. It is also important to realise that, as is shown below in the observational studies, the risks of thromboembolism in patients receiving baracitinib is similar to that which is expected in people with active RA.

Other JAK Inhibitors and Thromboembolism

There is very little information about thromboembolic risks in the tofacitinib trials in RA. Its overall risks of deaths and serious adverse events from a recent systematic review [23] is summarised in Table 1. However, potentially important new information is available from analyses of the Federal Drug Administration Adverse Event Reporting System (FAERs). An assessment by Verden et al [24] has evaluated adverse events reported for two formulations of tofacitinib and ruxolitinib. FAERS had 18 unique cases of pulmonary thrombosis for tofacitinib, 9 cases for ruxolitinib, and 3 cases for tofacitinib XR in which reporters identified these medications as the “Primary Suspect” drug. Sixteen of the 18 reported cases with tofacitinib were admitted to hospital. The Reporting Odds Ratio for pulmonary thrombosis was 2.46 (95% confidence intervals 1.55, 3.91) for tofacitinib; 1.46 (0.76, 2.80) for ruxolitinib; and 2.48 (0.80, 7.71) for tofacitinib XR. It is important to realise that post-marketing surveillance has several limitations in assessing risks. In particular new treatments are often given to patients with the worst forms of disease who have failed many previous treatments. It is possible such patients will have increased risks of thromboembolic diseases

irrespective of any treatment effects. When biologics were introduced prospective international registers were established to assess long-term treatment risks, but this has not been done to the same extent with JAK inhibitors.

Assessing the implications of this finding by itself is challenging. Pulmonary thrombosis occurs with some rare cardiac disorders [25] and vascular diseases like Behcet's syndrome [26]. There are historical reports of pulmonary thromboses superimposed upon prior pulmonary emboli [27]. Finally, some reports mix the terms pulmonary thrombosis and pulmonary embolism [28]. It is impossible to know whether some or all of these different factors are involved in the report from Verden et al. However, as most of the patients with pulmonary thromboses were admitted to hospital the diagnostic classification is likely to be based on expert assessments.

Finally, thromboembolism has been reported in a Phase 2 trial of another JAK inhibitor in RA [29]. This 12-week trial had two patients with pulmonary embolism out of 276 enrolled, both of whom were receiving different doses of the novel JAK inhibitor.

Thromboembolism and Rheumatoid Arthritis

The relationship between RA and thromboembolism has been extensively studied over the last decade. Observational studies have evaluated thromboembolic risks for RA patients in general, some sub-sets of RA patients such as rheumatoid factor positive patients, and patients taking some anti-rheumatic drugs. However, the studies do not give a comprehensive assessment of thromboembolic risks with treatment. Comparative data about risks from published studies is provided in Table 2. An early indication for a link was the observational study by Matta et al [30]. They evaluated thromboembolism in patients discharged from

short-stay hospitals in the United States between 1979 and 2005 who did not have surgery. Almost 5 million RA patients and nearly one billion controls were studied. Overall 0.85% of RA patients had a pulmonary embolus compared with 0.38% of controls. Deep venous thrombosis was diagnosed in 1.64% RA patients and 0.86% controls. In this study patients with RA had approximately double the thromboembolic risks.

A similar magnitude of risk was reported within the Rochester cohort of RA patients by Liang et al [31]. Their retrospective medical record review evaluated 609 RA patients followed over a decade or longer; the 30-year cumulative incidence rate of thromboembolic events was 7.2% compared to a risk of 3.5% in non-RA controls.

Several subsequent studies further evaluated this relationship [32-36]. Systematic reviews in RA [37] and other inflammatory rheumatic diseases [38] have combined the findings of these various studies. In RA, Ungprasert [37] evaluated 9 observational studies. The pooled risk ratios of venous thrombosis and pulmonary embolism in RA patients compared with non-RA controls was 2.08 (95 % confidence interval (CI) 1.75–2.47) and 2.17 (95 % CI 2.05–2.31), respectively. Risks were consistently increased across cohort, case–control, and cross-sectional studies. Lee and Pope [36] reported similar increased risks in 10 studies of RA patients with comparable high-risks in other inflammatory rheumatic diseases. More recent studies confirm the increased risk of thromboembolic disease in RA [39,40].

Meyer-Olesen et al [41] found high rheumatoid factor levels are a risk factor for deep venous thrombosis. They studied 54,628 participants from the Copenhagen City Heart Study. During 368,381 person-years, 670 individuals developed deep venous thrombosis. Individuals with

increased concentrations of rheumatoid factor had an up to 3-fold increased long-term risk and up to 9-fold increased 1-year risk.

Thromboembolism Risk with Biologics and Conventional DMARDs

Three case series reported links between thromboembolic events and treatment with tumour necrosis factor inhibitors [42-44]. A review suggested an immune-mediated mechanism of action [44]. Kim et al [40] completed a population-based cohort study based on USA insurance claims data. They analysed nearly 40,000 treatment episodes in nearly 30,000 RA patients. Hospitalisation for thromboembolism occurred in 5.5 per 1,000 person-years in biologic DMARD initiators and 4.4 in non-biologic DMARD initiators. The hazard ratio for thromboembolism in biologic DMARD initiators was highest in the first 180 days compared to non-biologic DMARD initiators at 2.48 (95% CI 1.14-5.39). They found no evidence that starting methotrexate without a biologic DMARD had an effect on thromboembolism risk.

In contrast, Davies et al [46] reported negative findings after evaluating data from the British Society for Rheumatology Biologics Register. They compared thromboembolic events in 11,881 RA patients starting any of the currently available tumour necrosis factor inhibitors (etanercept, infliximab or adaliumumab) with 3,673 patients treated with conventional DMARDs. They identified 196 first thromboembolic events. There was no difference in the rates of thromboembolic events between groups (adjusted hazard ratio 0.8; 95% CI 0.5-1.5). With all these observational studies a variety of sources of bias exist, including channelling bias in which “sicker” patients get newer treatments.

Non-Steroidal Anti-Inflammatory Drugs, Oral Corticosteroids and Thromboembolism

A prospective cohort study by Huerta et al [47], which involved a nested case-control analysis using the General Practice Research Database, evaluated thromboembolism risks in patients using corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). Thromboembolism was newly diagnosed in 6,550 patients. There were 10,000 matched controls. The cases and controls had a range of comorbid conditions; fewer than 3% had RA. The odds of having a pulmonary embolus increased with NSAIDs (odds ratio 1.85; 95% CI 1.65-2.10), particularly when treatment was started in the last 30 days. Risks were also increased by taking oral corticosteroids (odds ratio 3.05; 95% CI 2.51-3.69), with the risk also greatest in treatment started in the last 30 days.

Risks with NSAIDs were subsequently evaluated in a systematic review by Ungprasert et al [48]. Six cohort and case-control studies were indentified, in which 21,401 thromboembolic events were evaluated. The pooled risk ratio for thromboembolism in NSAID users was 1.80 (95% CI 1.28-2.52).

We have not found a comparable systematic review of thromboembolism with corticosteroids. However, recent observational studies suggest a relationship exists. A population-based case-control study by Johannesdottir et al [49] used national Danish databases. It compared 38,765 thromboembolism cases with 387,650 matched controls. Systemic glucocorticoids increased thromboembolic risks (adjusted incidence rate ratio 2.31; 95% CI 2.18-2.45). Risks were highest in new users. Waljee et al [50] evaluated American national private insurance claims for adults aged 18 to 64 years continuously enrolled from 2012 to 2014. In over one and a half million adults more than 20% had received at least one prescription for short term oral corticosteroids. Within 30 days of starting treatment

thromboembolism risks increased (incidence rate ratio 3.33; 95% CI 2.78-3.99). These rates increased with age.

Relative Frequency of Thromboembolism in the General Population

Table 2 provides information about thromboembolism risks (expressed as the number of events per 1,000 patient years) in the general population [51,52], compared with RA cases and controls. Rates of thromboembolism increase substantially with age, and also vary ethnically. Whilst caution is required when comparing these studies (owing to heterogeneity in the types of individuals enrolled and the manner in which RA was diagnosed), overall the balance of evidence suggests that in the general population and non-RA controls there are 1-4 thromboembolic events per 1,000 patient years. In RA, thromboembolic risks increase to 3-8 per 1,000 patient years. The impact of biologics and DMARDs on disease risk appears minimal, though corticosteroids may increase risks especially when treatment is initiated. Our previously stated estimate of the rate of thromboembolic events with 4mg baricitinib in trials of active RA (5 per 1,000 patient years) therefore falls within the expected range observed in RA patients irrespective of their treatment.

Challenges in Identifying Drug Risks in Rheumatoid Arthritis

It is important to consider the risks posed with novel drugs against those posed with existing treatments. None of the drugs used in RA is completely safe. Even paracetamol, which is widely used by many patients with RA, is associated with an increased overall mortality and a range of adverse events, with myocardial infarctions in some observational studies [53]. Historic studies have highlighted serious problems, including deaths, associated with long-established anti-rheumatic drugs, particularly NSAIDs and corticosteroids [54].

Methotrexate, which is the dominant DMARD in RA, can cause deaths due to bone marrow failure [55], interstitial lung disease [56] and inadvertent over-dosage [57]. Other DMARDs can also cause drug-related mortality. However, these risks must be weighed against the extensive evidence that effective treatment with methotrexate reduces overall mortality [58]. Although the risks of serious adverse events and excess mortality were a concern when biologics were introduced, there is robust evidence that they have overall beneficial effects with minimal evidence of excess mortality from receiving them [59].

Severe adverse reactions and deaths are relatively uncommon with anti-rheumatic drugs, including JAK inhibitors. However, the sizes of the clinical trials needed to define efficacy are insufficient to fully assess all the potential harms. In addition, trials often exclude patients who are older, frail, or have significant comorbidities; it is these individuals that are more likely to have significant adverse reactions to drugs but also more likely to suffer from thromboembolic disease. There are also major difficulties in distinguishing between the effects of RA and the impact of other drug treatments. In the case of biologics, establishing independent, long-term observational registries, was a crucial step in ensuring biologic treatment risks were not excessive. Similar approaches may be needed with new small molecule agents, like JAK inhibitors.

Conclusions

The publically available data suggests that in trials of baricitinib in RA there have been numerically more thromboembolic events in patients receiving active than control treatment, though there are too few patients to know if this difference is statistically significant. However, the risk of thromboembolism is small (about 5 events per 1,000 patient years) and appears comparable to the background risk observed in patients with RA (about 3-8 per 1,000

patient years). If one JAK inhibitor increases thromboembolic risks it is likely that this is a class effect and other JAK inhibitors may show risks. The observational study by Verden et al [24] suggests there may indeed be a general effect of JAK inhibitors on thromboembolic disorders, though there are ongoing uncertainties about its precise nature.

Concerns about thromboembolic risks with baricitinib are likely to have contributed to the FDA deciding to delay its approval. Such decisions are beyond academic review as regulators need to consider potential as well as actual risks. Uncertainties about risks with new treatments can be minimised by delaying approval so that further data can be accrued, though this has the disadvantage of also delaying patients accessing effective new treatments.

Manufacturers will undoubtedly wish to ensure full details of thromboembolic risks with JAK inhibitors are in the public domain as soon as possible. However, providing this information is unlikely to resolve uncertainties about the risks involved. The number of thromboembolic events will be small, patients enrolled in trials will not be representative of all RA patients likely to receive JAK inhibitors, and the amount of observational data outside trials is relatively limited. There is consequently a need for further large observational studies to accurately quantify thromboembolic risks attributable to new and existing drugs used to treat RA, and differentiate these from risks attributable to RA itself or its comorbidities. Until more information becomes available clinicians prescribing JAK inhibitors for RA ought to use these drugs cautiously in patients with pre-existing potential thromboembolic risks.

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Table 1 Thromboembolic Events, Deaths and Serious Adverse Events in Baricitinib Trials With Comparative Deaths And Serious Adverse Events From Systematic Review Of Tofacitinib

Authors	Trial	Year	Size	Duration	Thromboembolic Events		Deaths			Serious Adverse Events		
Baricitinib												
					Placebo	*Baricitinib 4mg*	*Placebo*	*Baricitinib 2mg*	*Baricitinib 4mg*	*Placebo*	*Baricitinib 2mg*	*Baricitinib 4mg*
Fleischmann et al [13]	RA-Begin	2017	588	12 months	Death from pulmonary embolism	-	3/210	-	0/374	20/201	-	29/374
Taylor et al [14]	RA-Beam	2017	1307	12 months	-	Thrombophlebitis	1/488	-	3/487*	22/488	-	23/487**
Dougados et al [15]	RA-Build	2017	684	6 months	-	Pulmonary embolism[a]	2/228	0/229	0/227	11/228	6/229	12/227
Tanaka et al [16]	Phase 2	2016	145	3 months	No thromboembolic events reported	-	0/49	0/24	0/24	1/49	1/24	0/24
Keystone et al [17]	Phase 2	2015	301	6 months			0/98	0/52	0/52	3/98	3/52***	0/52***
Genovese et al [18]	RA-Beacon	2016	527	6 months			0/176	0/174	1/177	13/176	7/174	18/177
Total					-	-	*6/1240 (0.5%)*	*0/479 (0%)*	*3/1341 (0.2%)*	*64/1240 (5.2%)*	*17/479 (3.5%)*	*82/1341 (6.1%)*
Tofacitinib												
					-	-	*Controls*	*Recommended Dose*	*High Dose*	*Controls*	*Recommended Dose*	*High Dose*
Tarp et al [23]	12 trials	2009-14	5801	2-24 months	-	-	2/1303 (0.2%)	6/1849 (0.3%)	3/2244 (0.1%)	72/1303 (5.5%)	126/1849 (6.8%)	130/2244 (5.8%)

*One death after switching from placebo to baricitinib 4mg

** 6-month data

*** 3-month data

[a]One additional pulmonary embolus in 28 day post-treatment follow up period

Note: no data is provided about thromboembolic events in some arms of the baricitinib trials and the systematic review of adverse events by Tarp et al [23]

Table 2. Frequency Of Thromboembolism Events In The Normal Population And In Patients With Rheumatoid Arthritis

Study	Year	Group	Size Of Study	Rate/1000 Patient Years
White [49]	2003	Normal population	From 6 major studies	1
Heit [50]	2015	Normal populations	From 11 major studies	1 to 2
Holmqvist et al [30]	2012	Controls	207,271 controls	2
Choi et al [31]	2013	Controls	95,776 controls	2
Kim et al [32]	2013	Controls	920,697 controls	3
Ogdie et al [37]	2017	Controls	1,225,571 controls	4
Bacani et al [33]	2012	RA	813 cases	7
Holmqvist et al [30]	2012	RA	45,490 cases	6
Choi et al [31]	2013	RA	9,589 cases	3
Kim et al [32]	2013	RA	92,827 cases	6
Yusuf et al [34]	2015	RA	70,768 RA cases	5
Kim et al [38]	2015	RA Biologics	5,920 cases	5
Ogdie et al [37]	2017	RA DMARD	31,336 cases	8
Kim et al [38]	2015	RA Methotrexate	17,614 cases	4
Ogdie et al [37]	2017	RA No DMARD	20,426 cases	7

DMARD=disease-modifying anti-rheumatic drug.