Thromboembolism with Janus Kinase (JAK) Inhibitor for Rheumatoid Arthritis: How Real is the Risk?

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Background and Objectives

- Two JAK inhibitors – baricitinib (BARI – Brand name: Olumiant) and tofacitinib (TOF – Brand name: Xeljanz) – provide rapid, effective oral treatment for RA and other inflammatory diseases

- Concerns about potential thromboembolic risks with JAK inhibitors
  - Clinical trials with BARI suggest possible increases in thromboembolisms
    - SPC for BARI was revised to include a warning of developing DVT and PE and that BARI should be used with caution in high-risk patients
  - Post-marketing surveillance with TOF suggest possible increases in PT

- This paper:
  - Reviews available evidence about thromboembolic events with BARI
  - Assesses thromboembolic risk with other JAK inhibitors
  - Considers challenges of unexpected AEs with new RA treatments

DVT, deep vein thrombosis; JAK, Janus kinase; PE, pulmonary embolism; PT, pulmonary thrombosis; SPC, summary of product characteristics.
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Thromboembolism in Absence of RA

Authors	Year	Group	Size	Rate/1000 PY
White[1]	2003	Normal population	From major studies	1
Heit[2]	2015	Normal populations	From 11 major studies	1–2
Holmqvist et al.[3]	2012	Controls	207 271 controls	2
Choi et al.[4]	2013	Controls	95 776 controls	2
Kim et al.[5]	2013	Controls	920 697 controls	3
Ogdie et al.[6]	2017	Controls	1 225 571 controls	4

Risk of thromboembolism in the general population and non-RA controls is 1–4 thromboembolic events per 1000 PY

PY, patient years

1. White R. Circulation 2003;107:I4–8. 2. Heit JA. Nat Rev Cardiol 2015;12:464–74. 3. Holmqvist ME, et al. JAMA 2012;308:1350–6. 4. Choi HK et al. Ann Rheum Dis 2013;72:1182–7.
5. Kim SC, et al. Arthritis Care Res 2013;65:1600–7. 6. Ogdie A, et al. Eur Heart J 2017. doi: 10.1093/eurheartj/ehx145.
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Thromboembolism in Patients with RA

Authors	Year	Group	Size	Rate/1000 PY
Bacani et al.[1]	2012	RA	813 cases	7
Holmqvist et al.[2]	2012	RA	45 490 cases	6
Choi et al.[3]	2013	RA	9 589 cases	3
Kim et al.[4]	2013	RA	92 827 cases	6
Yusuf et al.[5]	2015	RA	70 768 RA cases	5

Background risk of thromboembolism in patients with RA is about 3–7 per 1000 PY

PY, patient years

1. Bacani AK, et al. Arthritis Rheum 2012;64:53–61. 2. Holmqvist ME, et al. JAMA 2012;308:1350–6. 3. Choi HK et al. Ann Rheum Dis 2013;72:1182–7.
4. Kim SC, et al. Arthritis Care Res 2013;65:1600–7. 5. Yusuf HR, et al. Thromb Res 2015;135:50–7.
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Thromboembolism with RA Drugs

Authors	Year	Group	Size	Rate/1000 patient-years
Kim et al.[1]	2015	RA biologics	5 920 cases	5
Ogdie et al.[2]	2017	RA DMARD	31 336 cases	8
Kim et al.[1]	2015	RA MTX	17 614 cases	4
Ogdie et al.[2]	2017	RA no DMARD	20 426 cases	7

The impact of biologics and DMARDs on disease risk seems minimal, and the number of thromboembolic events is 4–8 per 1000 patient-years

1. Kim SC, et al. Arthritis Care Res 2013;65:1600–7. 2. Ogdie A, et al. Eur Heart J 2017. doi: 10.1093/eurheartj/ehx145.
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Overall Risks and Benefits of BARI

- Potential thromboembolic risks with BARI need to be considered in relation to its overall efficacy and toxicity in RA
- NMA of seven Phase 2 and 3 trials (N=3 461) found that:
  - Significantly more patients achieved ACR20 with BARI 4 mg + MTX or other DMARDs versus controls[1]
    - OR for achieving ACR20 was clinically important: 3.13 (CI 2.32 to 4.33)
  - Rates of TEAEs were similar between BARI and controls
- Non-systematic reviews supportive of efficacy and relative safety in active RA[2,3]
- Extension study and integrated analysis of all also confirm safety[4,5]
  - No new safety concerns to 5.5 years of treatment in 3 492 RA patients treated for 6 637 PY[6]

NMA, network meta-analysis; OR, odds ratio; PY, patient years; TEAE, treatment-emergent adverse event.

1. Lee YH, et al. Z Rheumatol 2017. doi: 10.1007/s00393-016-0254-4. 2. Richez C, et al. Expert Opin Pharmacother 2017;18:1399–407. 3. Kuriya B, et al. Ther Adv Musculoskelet Dis 2017;9:37–44. 4. Keystone EC, et al. J Rheumatol 2018;45:14–21. 5. Smolen J, et al. Ann Rheum Dis 2016;75(Suppl 2):243–4. 6. Genovese MC, et al. Arthritis Rheuamtol 2017;69:511. Scott IC, et al. Drug Safety 2018 Jul;41(7):645–53

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Thromboembolism with BARI

Authors	Trial	Year	Size	Duration (months)	Thromboembolic events		Deaths			SAEs		
					PBO	BARI 4 mg	PBO	BARI 2 mg	BARI 4 mg	PBO	BARI 2 mg	BARI 4 mg
Fleischmann et al.[1]	RA-BEGIN	2017	588	12	Death from PE	–	3/210	–	0/374	20/201	–	29/374
Taylor et al.[2]	RA-BEAM	2017	1307	12	–	Thrombo-phlebitis	1/488	–	3/487	22/488	–	23/487
Dougados et al.[3]	RA-BUILD	2017	684	6	–	PE*	2/227	0/229	0/227	11/228	6/229	12/227
Tanaka et al.[4]	Phase 2	2016	145	3	No events reported	–	0/49	0/24	0/24	1/49	1/24	0/24
Keystone et al.[5]	Phase 2	2015	301	6			0/98	0/52	0/52	3/98	3/52	0/52
Genovese et al.[6]	RA-BEACON	2016	527	6			0/176	0/174	1/177	13/175	7/174	18/177
Total					–	–	5/1240 (0.5%)	0/479 (0%)	3/1341 (0.2%)	64/1240 (5.2%)	17/479 (3.5%)	82/1341 (6.1%)

Three thromboembolic events were reported in six BARI trials: one control patient developed a fatal PE; one patient taking BARI 4 mg developed a PE and another developed thrombophlebitis; neither was fatal

PE, pulmonary embolus.

1. Fleischmann R, et al. Arthritis Rheumatol 2017;69:506–17. 2. Taylor PC, et al. N Engl J Med 2017;376:652–62. 3. Dougados M, et al. Ann Rheum Dis 2017;76:88–95.
4. Tanaka Y, et al. J Rheumatol 2016;43:504–11. 5. Keystone EC, et al. Ann Rheum Dis 2015;74:333–40. 6. Genovese MC, et al. N Engl J Med 2016;374:1243–52.
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Thromboembolism with other JAK Inhibitors

Authors	Trial	Year	Size	Thromboembolic events		Deaths			SAEs		
				Controls	Recommended dose	Controls	Recommended dose	High dose	Controls	Recommended dose	High dose
Tarp et al.[1]	Systematic review of 12 trials	2009–14	5801	–	–	2/1303 (0.2%)	6/1849 (0.3%)	3/2244 (0.1%)	72/1303 (5.5%)	126/1849 (6.38%)	130/2244 (5.8%)

- Assessment of data in FAERs identified[2]:
  - 18 unique cases of PT for TOF, 16 of which were admitted to hospital
    - OR for PT: 2.46 (95% CI 1.55 to 3.91)
  - 9 cases for RUX
    - OR: 1.46 (0.76 to 2.80)
  - 3 cases for TOF XR
    - OR: 2.48 (0.80 to 7.71)

Data from FAERs identified increased risks of PT with TOF, TOF XR, and RUX, although these findings should be viewed with caution due to limitations with post-marketing surveillance

FAERs, Federal Drug Administration Adverse Event Reporting System; JAK, Janus kinase; PT, pulmonary thrombosis; RUX, ruxolitinib; XR, extended release.

1. Tarp S, et al. Rheumatology 2017;56:417–25. 2. Verden A, et al. Drug Saf 2017. doi: 10.1007/s40264-017-0622-2.
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Challenges in identifying drugs risks in RA

- Risks of new drugs must be considered against the risks of existing treatments, none of which are completely safe
  - Paracetamol is associated with increased overall mortality and other AEs, including MI[1]
  - NSAIDs and corticosteroids associated with serious problems, including death[2]
  - MTX can cause deaths due to bone marrow failure, interstitial lung disease, and inadvertent overdose but reduces overall mortality[3–5]
  - Other DMARDs can cause drug-related mortality
  - Biologics have overall beneficial effects with minimal evidence of excess mortality[6]

- Severe ARs and deaths are relatively uncommon with anti-rheumatic drugs, including JAK inhibitors, but clinical trials:
  - To define efficacy are too small to assess all potential harms
  - Often exclude patients more likely to have reactions to drugs

AR, adverse reaction; JAK, Janus kinase; MI, myocardial infarction; MTX, methotrexate

1. Roberts E, et al. Ann Rheum Dis 2016;75:552–9. 2. Myllykangas-Luosujärvi R, et al. J Rheumatol 1995;22:2214–7. 3. Lim AY, et al. Rheumatology 2005;44:1051–5 . 4. Kinder AJ, et al. Rheumatology 2005;44:61–6. 5. Sinicina I, et al. J Rheumatol 2005;32:2009–11. 6. de La Forest Divonne M, et al. Jt Bone Spine 2017;84:133–40.
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Conclusion

- There are numerically more thromboembolic events in patients receiving BARI than control patients in RA
  - The estimated risk of thromboembolism with BARI (5 events per 1000 PY) is comparable to background risk in patients with RA (3–7 per 1000 PY)

- Given limitations with trial data, large observational studies are needed to
  - Accurately quantify thromboembolic risks attributable to new and existing RA drugs
  - Differentiate from risk attributable to RA or its comorbidities

- If one JAK inhibitor increases thromboembolic risks, it is likely that others may too
  - Clinicians prescribing JAK inhibitors for RA should use them cautiously in patients with pre-existing potential thromboembolic risks

PY, patient years

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