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JAK inhibitors in COVID-19: need for vigilance regarding increased inherent thrombotic risk

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There is accumulating evidence that COVID-19 is a hypercoagulable state. Reports of thrombotic events and autopsy findings of pulmonary thrombotic microangiopathy[1] in patients with COVID-19 are rising. Bompard *et al* recently reported a cohort study of 137 patients with COVID-19 pneumonia, in which retrospective review of computed tomography pulmonary angiography (CTPA) scans demonstrated a cumulative incidence of pulmonary emboli (PE) of 24% overall and 50% in intensive care[2]. Although it was initially thought that insidious venous thromboembolic events (VTE) were mainly confined to ventilated patients[3], we now understand thrombotic risk to be a wider problem in COVID-19. An overexuberant host inflammatory response, in selected patients with severe COVID-19, may contribute to the high mortality. We recently recommended screening for virally-driven hyperinflammation in COVID-19 and proposed that immunomodulation in this subgroup of patients, may improve outcomes[4]. There are several ongoing, randomised controlled trials evaluating the therapeutic potential of Janus Kinase inhibitors (JAKi) in severe COVID-19 (Table 1). JAKi have a purported advantage over other immunomodulatory strategies in COVID-19, as they may exert dual anti-inflammatory (blockade of multiple, pro-inflammatory cytokines simultaneously) and anti-viral effects (impeding cellular viral endocytosis[5,6]) and have convenient oral administration, with relatively short half-lives. JAKi may interrupt the signalling of several pro-inflammatory cytokines implicated in the pathogenesis of hyperinflammation, including interleukin (IL)-6, which has been the focus of several clinical trials in COVID-19. JAKi may also inhibit the entry of the SARS-CoV-2 virus into the AT2 alveolar epithelial cells; baricitinib (a JAK1/2 inhibitor), is a numb-associated kinase (NAK) inhibitor, with a particularly high affinity for AP2-associated protein kinase 1 (AAK1), a pivotal regulator of clathrin-mediated viral endocytosis[5]. We recommend vigilance to the potentially increased thrombotic risk associated with JAKi, given the hypercoagulability of COVID-19 and our recent thromboprophylaxis recommendations for all hospitalised patients with COVID-19[7].

Several JAKi are licenced in rheumatoid arthritis (RA) and have Food and Drug Administration (FDA) black-box warning for venous and arterial thrombotic events (including deep venous thrombosis (DVT), PE and ischaemic stroke) , resulting in dose restrictions (Table 1). It is unclear whether the presumed prothrombotic risks are dependent on JAK selectivity, drug specificity, dose or treatment duration or are confounded by indication. Whilst there is evidence of dose-dependent increased thrombotic risk associated with tofacitinib (five-fold increased risk of PE compared with tumour necrosis factor therapy

in RA)[8], a recent meta-analysis did not show an overall JAKi class pro-thrombotic signal[9]. Although a significantly increased incidence of thrombotic events (DVT and PE) was reported with bariticitinb in RA trials[10], this has not been observed in extension studies and recent trials in atopic dermatitis[11]. Post-marketing surveillance may delineate the true risk and whether this is disease-specific. It is unclear which JAK isoform (selectivity) confers impact on the efficacy or influences safety of these therapies for their licenced indications (e.g. rheumatoid arthritis) or in the new disease setting of COVID-19. It is important to note that at high doses, JAKi can become 'pan-JAK' inhibitors and exhibit non-selectivity[12]

Discussion continues regarding whether JAKi have a causal role in thrombotic events, or whether this represents a higher background thrombotic risk[13]. Indeed VTE risk in RA (0.3-0.7 /100 patient years) is greater compared with the general population (0.1-0.4 / 100 patient years)[13]. Intriguingly, ruxolitinib, unlike baricitinib, does not carry a VTE warning, despite both being selective JAK 1/2 inhibitors. Conversely there is a suggestion that ruxolitinib may lower the inherently raised thrombotic risk in myeloproliferative neoplasms[14]. Extrapolating this reassurance for ruxolitinib to COVID-19 is inappropriate as data for baricitinib and ruxolitinib is derived from different disease populations and their respective safety signals may be confounded by indication.

Clinical trials in COVID-19 using immunomodulation, including JAKi, intend to recruit patients with the most severe disease, and it is hypothesised that these patients are more hypercoagulable. We recommend risk mitigation strategies including consideration of exclusion of patients with high thrombotic risk, treatment with standard or intermediate-dose low molecular weight heparin prophlyaxis[7] during hospitalisation and consideration of extended-duration thromboprophylaxis after discharge from hospital, with monitoring for thromboses during the treatment and follow-up periods.

JAKi represent significant therapeutic advances, but are relatively new drugs with evolving safety profiles. Potential prothrombotic risk may be a class effect of JAKi, which is concerning given evidence of hypercoagulability with severe COVID-19. Cross-speciality communication is imperative when drug repurposing in the rapidly evolving pace of a pandemic.

Key Message 247 characters:
JAK inhibitors have promising therapeutic potential in COVID-19 with dual anti-inflammatory and anti-viral effects. We recommend vigilance to the potentially

increased thrombotic risk associated with JAKi, given the hypercoagulability of COVID-19.

Table 1. Summary of relevant licensed JAK inhibitors and thrombotic concerns

Summary of JAK inhibitor by selectivity, licensed indications, regulatory alerts regarding thrombosis and current trials in COVID-19. It is not clear if these trials excluded patients at risk of thrombosis or mandated thromboprophylaxis.

SmPC summary of medicinal product characteristics; FDA Food and Drug Administration; DVT deep venous thrombosis; PE pulmonary emboli; OD once daily; BD twice daily

JAK inhibitor and selectivity		**Pharmaceutical Company**	**Licensed indication**	**Notes regarding thrombosis**	**Trials in COVID-19** **N= 27 as of 18th May 2020**
JAK 1/2	Baricitinib	Eli Lilly	Rheumatoid arthritis	• August 2017: SmPC revised to include a warning of reports of DVT and PE in patients receiving baricitinib and advised caution for use in patients with risk factors for DVT/PE, such as older age, obesity, a medical history of these disorders, recent surgery or immobilisation • April 2018: FDA black-box warning for DVT PE, 2mg OD approved (not 4mg OD), due to thrombotic concerns	N= 11 NCT04340232; NCT04362943; NCT04346147; NCT04358614; NCT04390464; NCT04320277; NCT04373044; NCT04321993; NCT04345289; NCT04365764; NCT04366206
	Ruxolitinib	Novartis	Myelofibrosis; Polycythaemia	• No safety alert for thrombosis	N= 14 NCT04348071 NCT04355793 NCT04354714 NCT04362137 NCT04377620 NCT04334044 NCT04337359 NCT04331665 NCT04366232 NCT04374149 NCT04361903 NCT04338958 NCT04348695 NCT04359290
JAK 1/3	Tofacitinib	Pfizer	Rheumatoid arthritis; Psoriatic arthritis; Ulcerative Colitis	• February 2019: FDA issued safety alert concerning thrombotic risk • July 2019: FDA black-box warning for DVT and PE, for the 10mg BD dose (this higher dose is approved for ulcerative colitis) • November 2019: EMA updated European product information with warning for thrombosis	N= 2 NCT04390061 NCT04332042

JAK1	Upadacitinib	Abbvie	Rheumatoid arthritis	• August 2019: FDA black-box warning for DVT, PE and arterial thrombosis	None
JAK2	Fedratinib	Celgene	Myelofibrosis	• No safety alert for thrombosis	None

Author contribution:

PM drafted the manuscript**.** All authors contributed to discussions, revised and approved the manuscript.

Declarations of interest:

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