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References

1. Titanji BK, Farley MM, Mehta A, et al. Use of baricitinib in patients with moderate and severe COVID-19. Clin Infect Dis **2020**.
2. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet **2020**; 395:e30–1.
3. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis **2020**; 20:400–2.
4. Favalli EG, Biggioggero M, Maioli G, Caporali R. Baricitinib for COVID-19: a suitable treatment? [manuscript published online ahead of print 3 April 2020]. Lancet Infect Dis **2020**; S1473-3099(20)30262-0. doi:10.1016/S1473-3099(20)30262-0.
5. Center for Drug Evaluation and Research. US Food and Drug Administration. Medical review baricitinib. NDA 207-924. April 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207924Orig1s000MedR.pdf. Acessed 12 May 2020.
6. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost **2020**; 18: 1559-61. doi:10.1111/jth.14849. Epub 26 May 2020.
7. Vallejo-Yague E, Weiler S, Micheroli R, Burden AM. Thromboembolic safety reporting of tofacitinib and baricitinib: an analysis of the WHO VigiBase. Drug Saf **2020**;43:881-91. Available at: https://doi.org/10.1007/s40264-020-00958-9.

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Reply to Jorgensen et al

To the Editor—We read with interest the correspondence by Jorgensen et al in response to our recent publication in *Clinical Infectious Diseases* on the use of baricitinib for treatment of patients with moderate to severe coronavirus disease 2019 (COVID-19). The authors raise concerns on the potential impact of Janus kinase (JAK) inhibitors on COVID-19 coagulopathy, citing data on tofacitinib and baricitinib from the World Health Organization (WHO) Vigibase [1]. Several small cohort studies including cumulatively over 100 patients have reported on the use of the JAK ½ inhibitors baricitinib and ruxolitinib for the treatment of patients with COVID-19 [2–8]. Treatment duration in these studies ranged from 1 to 14 days, with no short-term toxicities reported with ruxolitinib dosing of 10–15 mg/day [4–6] and baricitinib dosing up to 8 mg/day [2]. The largest of these studies, a prospective longitudinal study in which 20 patients with COVID-19 received 4 mg baricitinib twice daily for 2 days followed by 4 mg daily for 7 days did not show a difference in the incidence of thrombotic events when compared to a control group of 56 individuals during the 1-month follow-up period [2]. Furthermore, recently published extended observation safety data for baricitinib in the treatment of rheumatoid arthritis (RA) with follow-up of up to 8.4 years found incidence rates for venous thromboembolism events (VTE) events between baricitinib dose groups (2 mg and 4 mg) to be comparable to those reported in patients with RA [9]. It remains unclear why in pooled data from clinical trials of baricitinib in RA, 6 individuals in the treatment group developed VTE; however, the long-term observational data are reassuring that this potential risk may not persist overtime [10]. Baricitinib in combination with remdesivir is being evaluated in a randomized, placebo-controlled trial (ACTT2) of COVID-19 treatment (NCT04401579), which has completed recruitment of over 1000 patients. VTE of any grade have been regularly monitored by the Data Safety and Monitoring Board (DSMB) for ACTT2. To date, the DSMB has not recommended unblinding or halting the trial, which is reassuring. This does not, however, preclude the possibility of an imbalance between arms that could emerge during the final trial analysis. Baricitinib through its immunomodulatory effects as highlighted by Jorgensen et al may in fact be beneficial in terms of reducing coagulopathy in patients with COVID-19, which is thought to be primarily mediated by hyperinflammation and endothelial damage. All of the cohort studies of baricitinib for COVID-19 treatment led to significant decline in inflammatory markers for patients who received the drug [2, 3, 8]. We agree that in the pursuit of effective therapeutics against COVID-19, there is a need to balance the potential adverse effects of any intervention with its hypothesized benefits and to perform randomized, controlled trials. Regarding baricitinib, ACTT2 should provide clarity on the VTE issue in the near future and its role in the treatment of COVID-19 in moderate to severe patients.

Notes

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References

1. Vallejo-Yagüe E, Weiler S, Micheroli R, Burden AM. Thromboembolic safety reporting of tofacitinib and baricitinib: an analysis of the WHO VigiBase. Drug Saf [Epub ahead of print]. Available at: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa879/5864596. Accessed 23 July 2020. doi: 10.1007/s40264-020-00958-9.
2. Bronte V, Ugel S, Tinazzi E, et al. Baricitinib restrains the immune dysregulation in COVID-19 patients. medRxiv [preprint] June 30, **2020**. [cited July 23, 2020, doi: 10.1101/2020.06.26.20135319
3. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in

COVID-19: a pilot study on safety and clinical impact. J Infect [Epub ahead of print]. Available at: https://www.journalofinfection.com/article/S0163-4453(20)30228-0/fulltext. Accessed 23 July 2020. doi: 10.1016j.jinf.2020.04.017.
4. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): a multicenter, single-blind, randomized controlled trial. J Allergy Clin Immunol **2020**; 146:137–46.e3.
5. Giudice V, Pagliano P, Vatrella A, et al. Combination of ruxolitinib and eculizumab for treatment of severe SARS-CoV-2-related acute respiratory distress syndrome: a controlled study. Front Pharmacol **2020**; 11:857.
6. La Rosée F, Bremer HC, Gehrke I, et al. The Janus kinase ½ inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. Leukemia **2020**; 34:1805–15.
7. Stebbing J, Krishnan V, de Bono S, et al. Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. EMBO Mol Med **2020**; e12697. [Epub ahead of print]. Available at: https://www.embopress.org/doi/full/10.15252/emmm.202012697. Accessed 23 July 2010, doi: 10.15252/emmm.202012697.
8. Titanji BK, Farley MM, Mehta A, et al. Use of baricitinib in patients with moderate and severe COVID-19. Clin Infect Dis **2021**; 72:1247–50.
9. Genovese MC, Smolen JS, Takeuchi T, et al. FRI0123 safety profile of baricitinib for the treatment of rheumatoid arthritis up to 8.4 years: an updated integrated safety analysis. Ann Rheum Dis **2020**; 79:642.
10. Taylor PC, Weinblatt ME, Burmester GR, et al. Cardiovascular safety during treatment with baricitinib in rheumatoid arthritis. Arthritis Rheumatol **2019**; 71:1042–55.

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Re: It Is Time to Address Airborne Transmission of COVID-19

To the Editor—We are concerned that the commentary by Morowska and Milton [1] has caused significant confusion. We agree that there is a gradient from large droplets to aerosols. We also agree that under experimental conditions and possibly in poorly ventilated, indoor, crowded environments there is potential for the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by aerosols. Furthermore, we agree that the availability of adequate ventilation indoors and the use of outdoor space have validity in preventing transmission. However, we argue that the epidemiologic data and clinical experience in managing the pandemic continue to support that the main mode of SARS-CoV-2 transmission is short range through droplets and close contact [2].

The concerns raised by the authors are not borne out in clinical experience. Long-range transmission beyond 2 meters in the more than 10 000 patients with coronavirus disease 2019 (COVID-19) hospitalized nationally in Canada and elsewhere seems rare at best. Current policies in many international jurisdictions recommend droplet/contact precautions for routine care of patients with suspected or confirmed COVID-19 and the addition of airborne precautions only for aerosol-generating medical procedures (AGMPs) [3]. Epidemiologic studies support this approach and even suggest that AGMP transmission risk may be overestimated [4].

In the case of the healthcare environment, we did not find any convincing evidence in their review to change occupational health and infection control practices. In contrast, real-world experiences have been published where, despite significant aerosol generation, rates of transmissions have been minimal. The first community-acquired COVID-19 case in the United States underwent multiple high-risk prolonged AGMPs [5]. Despite 121 exposures without N95 respirators, only 3 (2.5%) healthcare workers acquired SARS-COV-2, 2 of whom did not wear any respiratory protection at all and the third wore a surgical mask intermittently. In Singapore, 41 healthcare workers were exposed to multiple prolonged AGMPs in a COVID-19 patient, only 6 wore N95 respirators [6]. On serial testing, no staff acquired COVID-19. These observational case reports substantiate the Canadian experience in which COVID-19 patients are routinely managed with droplet/contact precautions; there has been no increased risk of infections in healthcare workers when compared with community populations [7].

Published case series of nonhealthcare settings confirm the findings of droplet/contact transmission, including a flight where only a single adjacent passenger was secondarily infected [8] and a cluster of infections at a call center related to close contact within a building [9], as well as multiple household contact studies with secondary attack rates of less than 20% [10].

Evidence-based policy around infection prevention should be informed by research from the physical sciences, biology, and epidemiology, with consideration of real-life aspects. We commend the authors for highlighting relevant experimental evidence. However, without reconciling with the clinical real-world experience of COVID-19, the authors draw premature conclusions about the importance of airborne transmission. This has resulted in confusion and fear in the general public, mistrust in healthcare workers, and a risk of a deepening divide between experimental scientists and healthcare epidemiologists.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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