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Authors' reply

Shelley Uppal and colleagues suggested that it cannot be concluded from our paper¹ that abrocitinib is effective and well tolerated in adolescents and adults with moderate-to-severe atopic dermatitis on the basis of the limitations of the JADE MONO-1 trial. We believe our conclusions are well supported by the design and results of the study.

Regarding the diagnostic criteria, the authors commented that the Hanifin and Rajka criteria are not suitable for population-based studies. However, JADE MONO-1 was a randomised, phase 3 study that included patients with a confirmed diagnosis of atopic dermatitis. Hence, the use of these criteria, which are universally recognised as the gold standard for the clinical diagnosis of atopic dermatitis, is appropriate.² Other diagnostic criteria for atopic dermatitis (UK working party and the American Academy of Dermatology criteria) are based on the Hanifin and Rajka criteria.² The authors also comment that the criteria might not be suitable for adults, yet they were developed focused on adult disease and are often unsuitable for paediatric use.³ The mean age of the overall population of JADE MONO-1 was 32.5 (SD 16.0) years, and the mean duration of atopic dermatitis since onset was 23.5 (SD 15.2) years. Therefore, most patients in JADE MONO-1 had an onset of atopic dermatitis before becoming adults. No specific diagnostic biomarkers have been identified for atopic dermatitis, but we hope that changes in the future.

Furthermore, in terms of the racial composition, most patients in JADE

MONO-1 were White, probably a result of the racial composition in the countries where the study sites were located. Including more Black patients in future trials will be important to fully represent the heterogeneity of atopic dermatitis. Yet, subpopulation analysis of JADE MONO-1 suggests that abrocitinib was effective in Black and White patients with atopic dermatitis. At week 12, more Black (n=32) and White (n=279) patients treated with abrocitinib (200 mg and 100 mg) versus placebo had an Investigator's Global Assessment response (Black patients, 27.3% for 200 mg and 53.3% for 100 mg vs 0%; White patients, 45.6% for 200 mg and 16.8% for 100 mg vs 9.8%) and 75% or more improvement from baseline in the Eczema Area and Severity Index score (Black patients, 36.4% for 200 mg and 66.7% for 100 mg vs 16.7%; White patients, 64.1% for 200 mg and 32.7% for 100 mg vs 13.1%).

We believe that abrocitinib was effective and well tolerated in adults and adolescents with moderate-to-severe atopic dermatitis. Currently ongoing studies will address the efficacy and safety of abrocitinib in other populations.

ELS is a consultant for Pfizer, AbbVie, Celgene, Eli Lilly, Galderma, GlaxoSmithKline, Menlo Therapeutics, LEO Pharma, and Regeneron; and a principal investigator for AbbVie, GlaxoSmithKline, LEO Pharma, Novartis, Regeneron, Tioga Pharmaceuticals, and Vanda Pharmaceuticals. TB is, or has been, a lecturer or a consultant, or both, for Pfizer, AbbVie, Allmiral, AnaptysBio, Arena, Asana Biosciences, Astellas, BioVerSys, Boehringer Ingelheim, Celgene, Daichi-Sankyo, Davos Biosciences, Dermavant/Roivant, DermTreat, DS Pharma, Evaxion, FLX Bio, Galapagos/MorphoSys, Galderma, Glenmark, GlaxoSmithKline, Incyt, Kymab, LEO Pharma, Eli Lilly, L'Oréal/LaRochePossay, Menlo Therapeutics, Novartis, Pierre Fabre, Sanofi-Regeneron, UCB, and Vectans. JPT is an adviser, investigator, or speaker for Pfizer, AbbVie, Eli Lilly, LEO Pharma, Regeneron, and Sanofi-Genzyme. HV is an employee and shareholder of Pfizer. RR is an employee and shareholder of Pfizer. This Correspondence was funded by Pfizer, in accordance with Good Publication Practice guidelines. We thank Juan Sanchez-Cortes for editorial and medical writing support.

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Using EM data to understand COVID-19 pathophysiology

The pathophysiology of multisystem inflammatory syndrome in children is not completely understood, but it is a field in COVID-19 under extensive investigation. Evidence of the effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on extra-pulmonary tissues is essential for understanding the disease's course and treatment.

We read with concern Carsten Dittmayer and colleagues' Correspondence,¹ in which they questioned the evidence of a viral particle shown in our recent Case Report² of a child with COVID-19-related multisystem inflammatory syndrome.

The ultrastructural evidence of SARS-CoV-2 in cardiac tissue was undisputed (a cardiomyocyte was shown in figure 3A, an endothelial cell was shown in figure 3C, and a neutrophil in figure 3D).² This finding was further corroborated by the detection of SARS-CoV-2 RNA by RT-PCR, and by immunohistochemistry.

We share Dittmayer and colleagues'¹ opinion that electron microscopy (EM) is the gold standard to prove the presence of an infectious unit and requires specialised staff. For

this reason, the EM in our report was done by a professor with more than 30 years of experience in ultrastructural analysis.^{3,4} Figure 3B in our case report² does show a rough endoplasmic reticulum, as suggested by Dittmayer and colleagues, but it also shows a particular aspect of viral particle assembly (a section through a spherical cluster of viral nucleocapsids apposed on the membrane of the rough endoplasmic reticulum), which is probably a viral translation centre.⁵

The presence of SARS-CoV-2 particles within membrane compartments, as shown by Dittmayer and colleagues,¹ is typical of preserved non-necrotic cells in which there is viral replication. In our Case Report, cells were undergoing necrotic degeneration (corroborated by C4d staining on figure 2D),² which led to cardiac failure and death. In this situation, viral particles might not appear in clusters within membranes but free in the cytosol, intermingled with organelle membranes undergoing fragmentation—much harder to recognise.

Although the criticism of one of the figures in our report does not affect the main message—that SARS-CoV-2 infection of cardiac tissue was probably a major contributor to the child's myocarditis and heart failure²—in our opinion, criticism of peer-reviewed published data should be more careful and preferentially addressed directly to the authors to avoid the spread of misleading information, clouding the scientific literature.

We declare no competing interests.

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Authors' reply

We fully agree with Marisa Dolhnikoff and colleagues that we should aim to understand COVID-19 pathophysiology. However, their arguments

directed at our Correspondence,¹ which should support their Case Report² on ultrastructural identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patient tissue, are not convincing. As in other fields of ultrastructural research, identification of subcellular structures is made on the basis of ultrastructural features, which are characteristic for each structure. The putative virus particles in the publication by Dolhnikoff and colleagues² lack essential and distinct ultrastructural features, such as biomembranes and surface

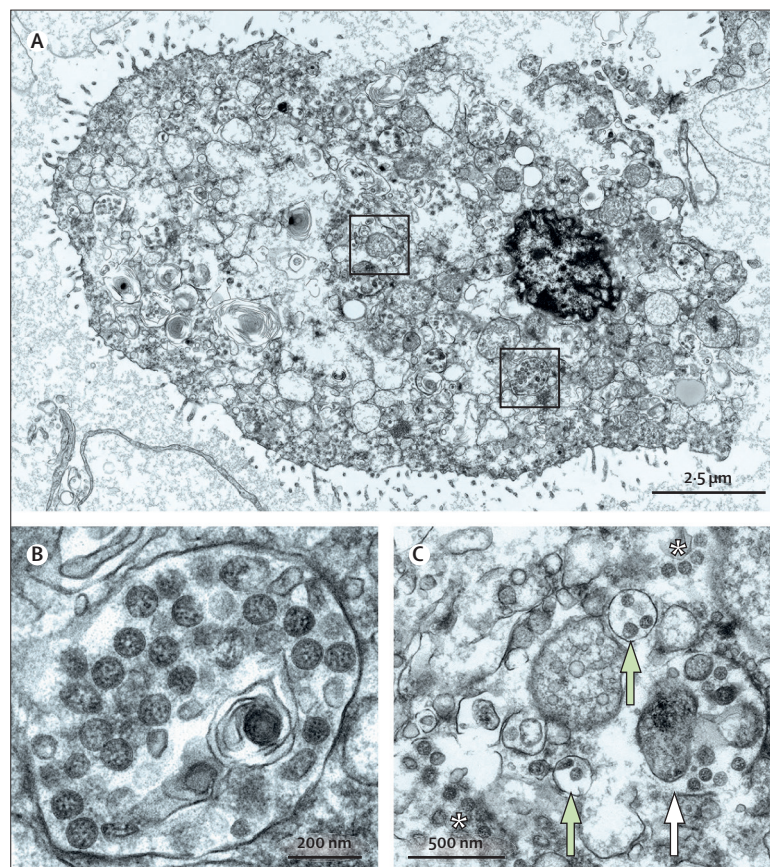


Figure: SARS-CoV-2 ultrastructural morphology in autolytic autopsy lung

In lung autopsy tissue showing marked autolysis, we found single cells with numerous well preserved SARS-CoV-2 particles. (A) The ultrastructure of the cell is severely affected and does not clearly identify the cell type. Boxed regions are magnified in panels B and C, in which many of the round and oval particles show characteristic morphological features of SARS-CoV-2. (C) The white asterisks show well preserved viral particles that appeared free within the cytoplasm, probably due to rupture of membrane compartments. The white arrow points to well preserved viral particles within ruptured membrane compartments, and the green arrows point to viral particles within intact membrane compartments. These images were acquired with a scanning electron microscope in transmission mode. A high-resolution dataset of the cell (A, C), digitised at 1 nm pixel size, is available online for open access pan-and-zoom analysis, also allowing for measurements of structures of interest to provide a positive control of coronavirus identification in autopsy tissue. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

For the high-resolution dataset see www.nanotomy.org