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Article:

Hoo, Z.H. orcid.org/0000-0002-7067-3783, Lai, L.Y.H., Sandler, R.D. et al. (4 more authors) (2023) Regarding the article entitled “Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis”. *Journal of Cystic Fibrosis*. ISSN 1873-5010

<https://doi.org/10.1016/j.jcf.2023.03.012>

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**REGARDING THE ARTICLE ENTITLED “EFFECT OF
ELEXACAFTOR/TEZACAFTOR/IVACAFTOR ON ANNUAL RATE OF LUNG FUNCTION
DECLINE IN PEOPLE WITH CYSTIC FIBROSIS”**

Running title:

Regarding the article on the effect of ELX/TEZ/IVA

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Dear Editor,

Lee et al [1] compared participants of ELX/TEZ/IVA clinical trials aged ≥ 12 years against 2012-2017 controls in the US CF Foundation Patient Registry. An annual ppFEV₁ trend of +0.39 (95% CI -0.06 to +0.89) for ELX/TEZ/IVA treated participants contrasted with -1.92 (95% CI -2.16 to -1.69) for controls. They concluded that ELX/TEZ/IVA is the first CF therapy that halts FEV₁ decline over a 2-year follow-up period, which included phases of lockdown/shielding due to the Covid-19 pandemic. The use of non-contemporaneous controls was suggested to have limited impact on the finding because a sensitivity analysis showed consistent results for 2012-2014 and 2015-2017 controls, and impact from Covid-19 lockdown/shielding on FEV₁ trend was unknown.

However, a recent Australian CF registry analysis [2] found an improvement in the annual ppFEV₁ trend from -0.13 (95% CI -0.36 to +0.11) to +1.76 (95% CI +1.46 to +2.05) during the Covid-19 pandemic among a largely CFTR modulator naïve population (only 0.4% on ELX/TEZ/IVA). A limitation is the inclusion of home spirometry readings during the Covid-19 pandemic. A previous study comparing FEV₁ trends for home versus clinic spirometry found a lack of precision with home spirometry but similar magnitude of FEV₁ trend [3]. If the Australian results are generalisable, contemporaneous controls not on ELX/TEZ/IVA may also have stable FEV₁. Recruitment for NCT03525444 and NCT03525548 trials commenced in June and August 2018, whilst the US lockdown started in March 2020 [4]. Therefore, all ELX/TEZ/IVA treated participants with 24-month follow-up had 3-13 months of their FEV₁ data collected during the Covid-19 lockdown, unlike the historical controls from 2012-2017. This may bias the analysis by Lee et al [1] in favour of ELX/TEZ/IVA treated participants.

Newsome et al [5] have previously pointed out bias in using historical cohorts as control groups to estimate the treatment effect of CFTR modulators. This is particularly problematic if the treatment follow-up coincided with Covid-19 pandemic which may be associated with a substantially improved FEV₁ trend even among people not using ELX/TEZ/IVA, probably from reduced exposure to respiratory viruses and a reduction in pulmonary exacerbations [2]. In estimating the treatment effect of ELX/TEZ/IVA, it may be more appropriate to use negative control outcomes combined with difference-in-differences analysis as proposed by Newsome et al [5] instead of comparison against historical cohorts. Longer-term follow-up of ELX/TEZ/IVA treated participants in the post-Covid epoch is also important, as people with CF start returning to their pre-pandemic lifestyle.

COMPETING INTERESTS

None declared.

REFERENCES

- [1] Lee T, Sawicki GS, Altenburg J, et al. Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis. *J Cyst Fibros* 2022 [Epub ahead of print]
- [2] Doumit M, Chuang S, Middleton P, et al. Clinical outcomes of adults and children with cystic fibrosis during the Covid-19 pandemic. *J Cyst Fibros* 2022 [Epub ahead of print]
- [3] Paynter A, Khan U, Heltshe SL, Goss CH, Lechtzin N, Hamblett NM. A comparison of clinic and home spirometry as longitudinal outcomes in cystic fibrosis. *J Cyst Fibros* 2022;21:78–83.
- [4] Centers for Disease Control and Prevention. CDC museum Covid-19 timeline. Published August 2022.
<https://www.cdc.gov/museum/timeline/covid19.html#:~:text=March%2015%2C%202020,the%20spread%20of%20COVID%2D19>. Date last accessed: March 8 2023.
- [5] Newsome SJ, Daniel RM, Carr SB, Bilton D, Keogh RH. Using negative control outcomes and difference-in-differences analysis to estimate treatment effects in an entirely treated cohort: the effect of ivacaftor in cystic fibrosis. *Am J Epidemiol* 2022;191:505–15.