EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
F. BECQ ET AL.

The rescue of F508del-CFTR by elexacaftor/tezacaftor/ivacaftor (Trikafta) in human airway epithelial cells is underestimated due to the presence of ivacaftor

Frédéric Becq[1], Sandra Mirval[1], Thomas Carrez[1,2], Manuella Lévêque[1], Arnaud Billet[1], Christelle Coraux[3], Edouard Sage[4,5] and Anne Cantereau[1]

[1]Laboratoire Signalisation et Transports Ioniques Membranaires, Université de Poitiers, Poitiers, France. [2]ManRos therapeutics, Presqu'île de Perharidy, Roscoff, France. [3]INSERM UMR-S 1250, Université de Reims-Champagne Ardenne, Reims, France. [4]INRAE UMR 0892, Université Versailles-Saint-Quentin-en-Yvelines, Versailles, France. [5]Service de Chirurgie Thoracique et Transplantation Pulmonaire, Hôpital Foch, Suresnes, France.

Corresponding author: Frédéric Becq (frederic.becq@univ-poitiers.fr)

Shareable abstract (@ERSpublications)
Ivacaftor is not able to potentiate the function of Trikafta-rescued F508del-CFTR due to its destabilising effect. Ivacaftor does not preclude the use of different potentiators combined with Trikafta, so the beneficial effect of Trikafta is underestimated. https://bit.ly/3dxlsJb

Cite this article as: Becq F, Mirval S, Carrez T, *et al*. The rescue of F508del-CFTR by elexacaftor/tezacaftor/ivacaftor (Trikafta) in human airway epithelial cells is underestimated due to the presence of ivacaftor. *Eur Respir J* 2022; 59: 2100671 [DOI: 10.1183/13993003.00671-2021].

This article has an editorial commentary: https://doi.org/10.1183/13993003.02380-2021

Received: 5 March 2021
Accepted: 25 June 2021

Abstract

Trikafta, currently the leading therapeutic in cystic fibrosis (CF), has demonstrated a real clinical benefit. This treatment is the triple combination therapy of two folding correctors elexacaftor/tezacaftor (VX445/VX661) plus the gating potentiator ivacaftor (VX770). In this study, our aim was to compare the properties of F508del-CFTR in cells treated with either lumacaftor (VX809), tezacaftor, elexacaftor, elexacaftor/tezacaftor with or without ivacaftor. We studied F508del-CFTR function, maturation and membrane localisation by Ussing chamber and whole-cell patch-clamp recordings, Western blot and immunolocalisation experiments. With human primary airway epithelial cells and the cell lines CFBE and BHK expressing F508del, we found that, whereas the combination elexacaftor/tezacaftor/ivacaftor was efficient in rescuing F508del-CFTR abnormal maturation, apical membrane location and function, the presence of ivacaftor limits these effects. The basal F508del-CFTR short-circuit current was significantly increased by elexacaftor/tezacaftor/ivacaftor and elexacaftor/tezacaftor compared to other correctors and nontreated cells, an effect dependent on ivacaftor and cAMP. These results suggest that the level of the basal F508del-CFTR current might be a marker for correction efficacy in CF cells. When cells were treated with ivacaftor combined to any correctors, the F508del-CFTR current was unresponsive to the subsequently acute addition of ivacaftor, unlike the CFTR (cystic fibrosis transmembrane conductance regulator) potentiators genistein and Cact-A1 which increased elexacaftor/tezacaftor/ivacaftor and elexacaftor/tezacaftor-corrected F508del-CFTR currents. These findings show that ivacaftor reduces the correction efficacy of Trikafta. Thus, combining elexacaftor/tezacaftor with a different potentiator might improve the therapeutic efficacy for treating CF patients.