Dual CFTR modulator therapy efficacy in the real world: lessons for the future

Anna-Maria Dittrich [1] and Sandra Y. Chuang [2,3]

[1]Department for Pediatric Pneumology, Allergy and Neonatology, Hannover Medical School (MHH), Hannover, Germany. [2]Discipline of Paediatric and Child Health, School of Clinical Medicine, University of New South Wales, Sydney, NSW, Australia. [3]Respiratory Medicine Department, Sydney Children's Hospital, Randwick, NSW, Australia.

Corresponding author: Anna-Maria Dittrich (Dittrich.anna-maria@mh-hannover.de)

Shareable abstract (@ERSpublications)
Stringent analyses caution against drawing conclusions about the real-world efficacy of CFTR modulator therapy too early https://bit.ly/3dJt6no

Cite this article as: Dittrich A-M, Chuang SY. Dual CFTR modulator therapy efficacy in the real world: lessons for the future. *ERJ Open Res* 2022; 8: 00464-2022 [DOI: 10.1183/23120541.00464-2022].

Received: 16 Sept 2022
Accepted: 21 Sept 2022

Few diseases have undergone such transformative changes in the past four decades as cystic fibrosis. Cystic fibrosis has become the first example of the successful development of mutation-specific drugs. These drugs, known as cystic fibrosis transmembrane conductance regulator (CFTR) modulators, which improve the function of the CFTR channel, have been able to advance incrementally the overall positive development of therapeutic options in cystic fibrosis in only the last 10 years [1].

In the case of the CFTR modulator with the longest licensing history, ivacaftor (IVA), several studies recapitulate the impressive results from clinical trials in real-world data [2, 3] and demonstrate long-term benefit, affecting such hard endpoints as survival and lung transplantation [4, 5]. Today, three combination therapies, lumacaftor (LUM)/IVA, tezacaftor (TEZ)/IVA and elexacaftor (ELX)/TEZ/IVA, have proven efficacy in clinical trials for patients with an F508del homozygous mutation combination [6–8] and other mutations in combination with F508del heterozygous status [9–11], extending access to CFTR modulators to well above 75% of all cystic fibrosis patients. Studies addressing the long-term effects of these three combination therapies in real life are less frequent than for IVA, though. Due to later licensing, so far, these studies also typically lack the duration of studies addressing IVA. Moreover, they provide conflictive results, such as those concerning trajectories of forced expiratory volume in 1 s (FEV_1) % pred [12, 13] and the reduction of pulmonary exacerbations (PEx) [13, 14].

In their article in this issue of *ERJ Open Research*, Muilwijk *et al*. [15] assessed longitudinal clinical trajectories before and after introduction of dual CFTR modulators (all on LUM/IVA for the first 2 years, then approximately half transitioned from LUM/IVA to TEZ/IVA) in a large cohort of 401 F508del homozygous cystic fibrosis patients ⩾12 years of age by extracting annualised data from the Dutch cystic fibrosis registry between 2010 and 2019. The authors' analyses are commendable due to the large group of patients and the length of observation period included. The authors' inclusion of a large, heterogeneous group of patients and a fairly long observation period (up to 3 years post commencement of dual CFTR modulators) counterbalances the limitations of their registry-based analyses, particularly their lack of encounter-based data and the large number of missing data regarding intravenous antibiotic use. Due to the longitudinal nature of the study and the extended observation periods of >12 months compared to previous real-world studies, Muilwijk *et al*. [15] was able to establish not only the absolute change in FEV_1 % pred over time but also the long-term trajectory associated with dual CFTR modulator use. Muilwijk *et al*. [15] demonstrated that dual CFTR modulator initiation permits smaller but significant acute FEV_1 % pred gains compared to phase III clinical trials and improves FEV_1 % pred trajectories for all people with cystic fibrosis (pwCF) included in their analysis over the course of 3 years. Furthermore, initiation of dual CFTR modulator had positive effects on body mass index (BMI) trajectories in pwCF <19 years of age and led to an impressive three-fold reduction in *i.v.* antibiotic duration in the first year

after therapy initiation but not thereafter. Their subgroup analyses are encouraging in that the reduction in the rate of FEV_1 % pred decline is observed not only in the population of patients with a FEV_1 between 40% and 90% pred, which represent the subgroup included in phase III clinical trials, but also patients with FEV_1 <40% pred, where it trends even higher (0.81% *versus* 1.4%). Furthermore, except for the BMI trajectories where effects were more pronounced in pwCF <19 years of age and acute BMI gains where females showed 0.33 higher improvements compared to males (p=0.018), the subgroup analyses provided no indication that long-term dual CFTR modulator effects are affected by age, sex or clinical status before initiation of therapy.

But are dual CFTR modulator effects really age- and sex-agnostic, and not affected by the range of sequelae that cystic fibrosis disease has caused before they are initiated in an individual patient?

Observational and read-world studies on IVA in pwCF with gating mutation [16–18] refute this optimistic outlook. Sex differences have been observed for IVA with females showing larger reductions in sweat chloride than males [19, 20] and larger reductions in the annualised PEx rate [20]. The differential effects on sweat Cl^- are of particular interest taking into account the first longitudinal analysis of real-world data on ELX/TEZ/IVA, which identified a significant correlation between sweat Cl^- reductions and FEV_1 % pred improvements after 6 months of therapy [21]. In addition, FEV_1 % pred response to LUM/IVA in adolescents correlates with age at initiation where lower age at initiation was associated with greater FEV_1 % pred change [22]. Registry data from children and adolescents also suggests that younger age at initiation of IVA leads to improved preservation of lung function and a larger impact on PEx [23]. Furthermore, the improvements in pancreatic function observed in very young patients initiating IVA or LUM/IVA [17, 18, 24, 25] suggest that age at initiation of CFTR modulator therapy does matter at least concerning specific organ functions.

Given this, it is interesting that Muilwijk *et al*. [15] refute their own results obtained in a smaller study (n=97 *versus* n=401) with a similar follow-up time post-dual CFTR modulator initiation (median follow up time 2.7 *versus* 2.1 years) [13]. In this analysis, they failed to detect significant improvements on a group level with regards to FEV_1 % pred and PEx after initiation of LUM/IVA [13]. These differences indicate an important caveat of real-world observational studies where small effects might be lost in the heterogeneity of cystic fibrosis if insufficient numbers of pwCF are interrogated. Such analyses are even more challenging regarding treatments such as LUM/IVA or TEZ/IVA, the effects of which on critical read-out parameters such as FEV_1 % pred were small even in the phase III clinical trials [6, 7].

The stringent analyses by Muilwijk *et al*. [15] in this issue of *ERJ Open Research* thus caution to draw conclusions about real-world efficacy of CFTR modulator therapy too early. Patience is warranted and definitive answers to age- and sex-specific differences as well as the impact of clinical status upon initiation might have to wait until more patients have been started on specific CFTR modulators or more time has passed to allow differences to become discernible. Particularly, less pronounced pharmacological effects on specific endpoints might necessitate larger numbers of pwCF to identify differences than available for analyses from open-label extension or registry-based studies today. Cystic fibrosis is a highly heterogeneous disease, encompassing different phenotypes, trajectories and organ systems. Rarely are there medications that benefit all patients equally well and there is no reason to believe that CFTR modulators behave any differently than any other medication. Finally, we must not forget that clinical improvements will lead to different approaches towards reductions in therapy, in turn influencing long-term responses to CFTR modulators. While for pwCF, therapy reduction most likely ranks higher than many other treatment goal, their effect will make the analysis of real-world data even more challenging. Therefore, it is encouraging that after licensing of the latest CFTR modulator combination therapy, ELX/TEZ/IVA [8], concerted efforts have been made to rapidly advance several real-world observational studies as well as studies addressing therapy reduction through controlled, pre-specified and randomised approaches. While the data of Muilwijk *et al*. [15] probably do not yet provide definitive answers to pressing questions, their questions draw our attention to the research that lies ahead. As more CFTR modulators come into clinical use, it is important to develop now the questions and tools to interrogate therapeutic responses to these ground-breaking new medications. Only then can we make the most of these exciting new therapies, as such analyses will direct future CFTR-restoring research and patient care with the ultimate goal to offer each person with cystic fibrosis the most effective therapy possible.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: A-M. Dittrich has received grants from Vertex, and the German Federal Ministry of Education and Research, outside the submitted work. S.Y. Chuang is an associate editor of this journal.

References

1 Bell SC, Mall MA, Gutierrez H, *et al.* The future of cystic fibrosis care: a global perspective. *Lancet Respir Med* 2020; 8: 65–124.
2 Volkova N, Moy K, Evans J, *et al.* Disease progression in patients with cystic fibrosis treated with ivacaftor: data from national US and UK registries. *J Cyst Fibros* 2020; 19: 68–79.
3 Guimbellot J, Solomon GM, Baines A, *et al.* Effectiveness of ivacaftor in cystic fibrosis patients with non-G551D gating mutations. *J Cyst Fibros* 2019; 18: 102–109.
4 Bessonova L, Volkova N, Higgins M, *et al.* Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. *Thorax* 2018; 73: 731–740.
5 Kirwan L, Fletcher G, Harrington M, *et al.* Longitudinal trends in real-world outcomes after initiation of ivacaftor. A cohort study from the cystic fibrosis registry of Ireland. *Ann Am Thorac Soc* 2019; 16: 209–216.
6 Wainwright CE, Elborn JS, Ramsey BW, *et al.* Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med* 2015; 373: 220–231.
7 Taylor-Cousar JL, Munck A, McKone EF, *et al.* Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del. *N Engl J Med* 2017; 377: 2013–2023.
8 Heijerman HGM, McKone EF, Downey DG, *et al.* Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet* 2019; 394: 1940–1948.
9 Rowe SM, Daines C, Ringshausen FC, *et al.* Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis. *N Engl J Med* 2017; 377: 2024–2035.
10 Middleton PG, Mall MA, Drevinek P, *et al.* Elexacaftor-Tezacaftor-Ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med* 2019; 381: 1809–1819.
11 Barry PJ, Mall MA, Alvarez A, *et al.* Triple therapy for cystic fibrosis Phe508del-gating and -residual function genotypes. *N Engl J Med* 2021; 385: 815–825.
12 Mesinele J, Ruffin M, Guillot L, *et al.* Lumacaftor/ivacaftor in people with cystic fibrosis: factors predisposing the response and impact on lung function decline. *J Cystic Fibrosis* 2022; 21: Suppl. 1, S13.
13 Muilwijk D, Bierlaagh M, van Mourik P, *et al.* Prediction of real-world long-term outcomes of people with CF homozygous for the F508del mutation treated with CFTR modulators. *J Pers Med* 2021; 11: 1376.
14 Konstan MW, McKone EF, Moss RB, *et al.* Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med* 2017; 5: 107–118.
15 Muilwijk D, Zomer-van Ommen DD, Gulmans VAM, *et al.* Long-term effectiveness of dual CFTR modulator treatment of cystic fibrosis. *ERJ Open Res* 2022; 8: 00204-2022.
16 Davies JC, Wainwright CE, Sawicki GS, *et al.* Ivacaftor in infants aged 4 to <12 months with cystic fibrosis and a gating mutation. Results of a two-part phase 3 clinical trial. *Am J Respir Crit Care Med* 2021; 203: 585–593.
17 Rosenfeld M, Wainwright CE, Higgins M, *et al.* Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. *Lancet Respir Med* 2018; 6: 545–553.
18 Davies JC, Cunningham S, Harris WT, *et al.* Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2–5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. *Lancet Respir Med* 2016; 4: 107–115.
19 Aalbers BL, Hofland RW, Bronsveld I, *et al.* Females with cystic fibrosis have a larger decrease in sweat chloride in response to lumacaftor/ivacaftor compared to males. *J Cyst Fibros* 2021; 20: e7–e11.
20 Secunda KE, Guimbellot JS, Jovanovic B, *et al.* Females with cystic fibrosis demonstrate a differential response profile to ivacaftor compared with males. *Am J Respir Crit Care Med* 2020; 201: 996–998.
21 Nichols DP, Paynter AC, Heltshe SL, *et al.* Clinical effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: a clinical trial. *Am J Respir Crit Care Med* 2022; 205: 529–539.
22 Bui S, Masson A, Enaud R, *et al.* Long-term outcomes in real life of lumacaftor-ivacaftor treatment in adolescents with cystic fibrosis. *Front Pediatr* 2021; 9: 744705.
23 Merlo C, McGarry L, Thorat T, *et al.* Initiating ivacaftor (IVA) at younger vs older ages improves pulmonary outcomes in people with cystic fibrosis (pwCF): a long-term real-world study. *J Cystic Fibrosis* 2022; 21: Suppl. 1, S33–S34.
24 McNamara JJ, McColley SA, Marigowda G, *et al.* Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2–5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. *Lancet Respir Med* 2019; 7: 325–335.
25 Rayment JH, Asfour F, Rosenfeld M, *et al.* A phase 3, open-label study of lumacaftor/ivacaftor in children 1 to less than 2 years of age with cystic fibrosis homozygous for F508del-CFTR. *Am J Respir Crit Care Med* 2022; in press [https://doi.org/10.1164/rccm.202204-0734OC].