



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

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Stringent analyses caution against drawing conclusions about the real-world efficacy of CFTR modulator therapy too early <https://bit.ly/3dJt6no>

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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 (FEV₁) % 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 FEV₁ % 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 FEV₁ % pred gains compared to phase III clinical trials and improves FEV₁ % 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 FEV₁ % pred decline is observed not only in the population of patients with a FEV₁ between 40% and 90% pred, which represent the subgroup included in phase III clinical trials, but also patients with FEV₁ <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 real-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 FEV₁ % pred improvements after 6 months of therapy [21]. In addition, FEV₁ % pred response to LUM/IVA in adolescents correlates with age at initiation where lower age at initiation was associated with greater FEV₁ % 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 MUIJLWIJK *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 FEV₁ % 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 FEV₁ % pred were small even in the phase III clinical trials [6, 7].

The stringent analyses by MUIJLWIJK *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 MUIJLWIJK *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.

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