Individualized approach to elexacaftor/ tezacaftor/ ivacaftor dosing in cystic fibrosis

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ABSTRACT

The prevalence of mental health disorders is high in people with cystic fibrosis, and psychological symptoms in CF have been linked to poor treatment adherence, worse treatment outcomes, and greater health utilization and cost.

Recently, The increased availability of CFTR modulators is revolutionizing CF care by augmenting the CFTR protein with downstream benefits.
Over the last 3 years, we have initiated elexacaftor/tezacaftor/ivacaftor (ETI) in 127 patients in our clinic.
In a small group of our patients [10 patients/ 7.9% of patients on elexacaftor/tezacaftor/ivacaftor] who developed self-reported worsening anxiety, irritability and/or mental slowness shortly after initiation of full-dose treatment, we adopted a dose-reduction strategy.
Full dose ETI resulted in 13.9 points improvement in mean ppFEV1 compared to baseline (p=0.0164), and mean of difference in sweat chloride was -39.3mmol/L.
Follow-up data recorded for up-to 24 weeks after dose reduction, resulted in resolution of self-reported mental/psychological side-effects, while their clinical parameters were comparable to their data on original full dose (mean ppFEV-1 83.4% on reduced dose compared to mean ppFEV-1 of 80.3% on full standard dose, and mean sweat chloride was 32.2mmol/L and 33.4mmo/L on reduced dose and full dose, respectively).

Our approach suggests that it may be feasible and important to reduce treatment dose to alleviate side-effects, without loss of clinical effectiveness, though prospective monitoring to ensure sustained benefits is critical and ongoing.

INTRODUCTION

➢Mental health and neurocognitive adverse events have been reported with all available CFTR modulators *(Talwalkar et al. 2017; Dagenais, Su, and Quon 2020)*;
- ✓(ETI) elexacaftor/tezacaftor /ivacaftor *(Tindell et al. 2020; Heo et al. 2022; S. G, G. L, P. K et al. 2022)*
- ✓lumacaftor/ivacaftor (*Burgel et al. 2020; McKinzie et al. 2017)*
- ✓tezacaftor/ivacaftor *(Perez et al. 2019)*

➢ Current recommended standard dose of ETI is two tablets of elexacaftor/tezacaftor/elexacaftor (200/100/150mg) in the morning and one tablet of ivacaftor 150mg in the evening, based on data from a phase II and subsequent phase III clinical trials that demonstrated an improvement in percentage of predicted FEV_1 by 10 to 14.3 points, reduction in pulmonary exacerbations by 63%, an improvement in respiratory domain score on the Cystic Fibrosis Questionnaire-Revised (CFQ-R) by 17.4 to 20.2 points, and a sweat chloride concentration that was 41.8 to 45 mmol per liter lower on the standard dose of ETI *(Middleton et al. 2019, Heijerman et al. 2019).*

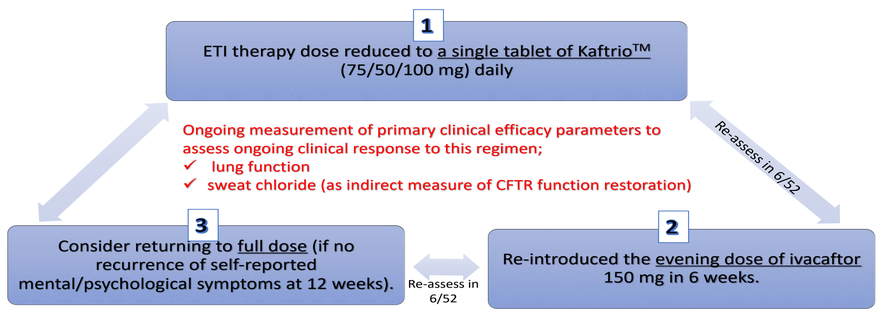
➢ Phase 2 clinical trials demonstrated a variable but clinically significant response to different doses of the triple CFTR Modulator elexacaftor/tezacaftor/ivacaftor. Doses as low as 50mg of VX-445 (elexacaftor) resulted in improvements in FEV1 and Sweat chloride of almost 11% and -38mmol/L respectively *(Keating et al. 2018)*

➢phase 3b clinical trial of ETI;
3 out of 87 participants in ETI group discontinued treatment due to psychological adverse events *(Sutharsan et al. 2022)*

➢Incidence of mental health and/or neurocognitive adverse events appear to be higher after initiation of ETI compared to other CFTR modulators (Our real-world experience)

➢Consequences of psychological symptoms CF;
- ✓Poor treatment adherence *(Smith et al. 2010; Hilliard et al. 2015)*.
- ✓Worse clinical outcomes *(Ploessl, Pettit, and Donaldson 2014; Snell et al. 2014; Quittner et al. 2016)*.
- ✓*Greater health care utilization and costs (Snell et al. 2014)*

Dose reduction protocol



Response to dose reduction

➢A total of 10 patients (7.9% of patients on ETI therapy) developed self-reported anxiety, irritability and/or mental slowness shortly after initiation of full-dose treatment.
➢None of these patients reported any anxiety or depression prior to ETI or were taking psychotropic medications
➢Full dose ETI resulted in;
- ✓13.9 points improvement in mean $ppFEV_1$ (p=0.0164),
- ✓Mean of difference in sweat chloride was -39.3mmol/L

Consistent with clinical trial finding *(Middleton et al. 2019; Heijerman et al. 2019; Barry et al. 2021)*

➢A total of 9 patients commenced on the dose reduction protocol, one patient opted to discontinue ETI and switched back to his original monotherapy modulator ivacaftor
➢Dose reduction resulted in resolution of self-reported mental/psychological side-effects.
➢Clinical parameters were comparable to their data on original full dose (figure 1 &2):

	Full standard ETI dose	Reduced ETI dose
Mean ppFEV-1	80.3%	83.4%
Mean Sweat Chloride	33.4mmol/l	32.2mmol/l

➢Repeat Ultra-Low Dose CT scans in patients who completed 24 weeks on reduced dose regimen (total of 2 patients) showed significant response compared to imaging before initiation of modulation therapy (figure 3&4)

Figure 1 Change in FEV1 % predicted at baseline, on full standard-dose, and reduced-dose of elexacaftor/ tezacaftor/ ivacaftor therapy

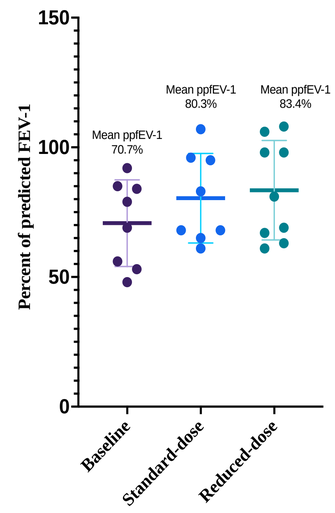


Figure 2 Change in sweat chloride at baseline, on full standard-dose, and reduced-dose of elexacaftor/ tezacaftor/ ivacaftor therapy

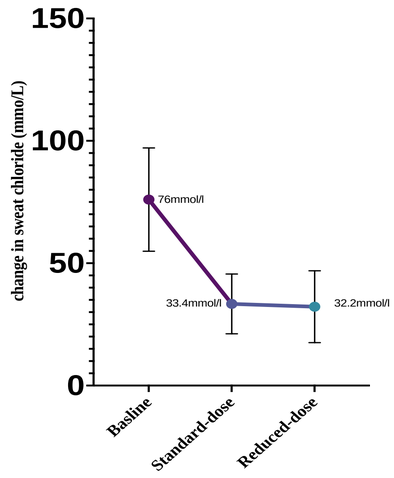


Figure 3: (Patient 1) Ultra-Low Dose CT Thorax pretreatment (A) and 24 weeks post modified dose regimen(B)

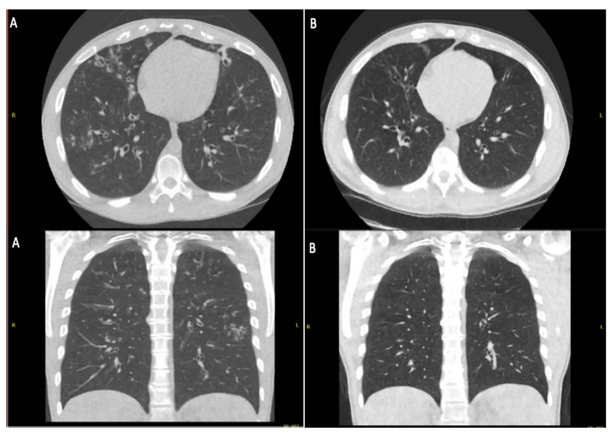
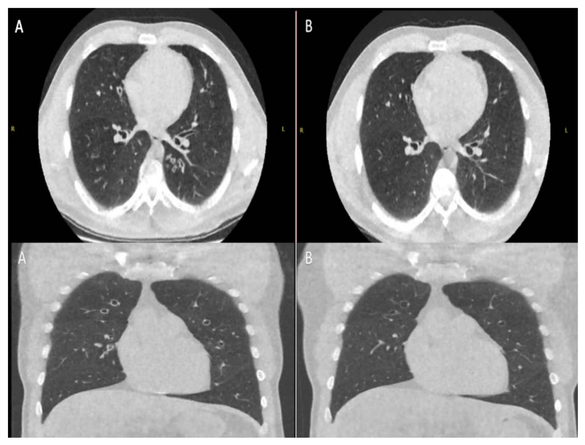


Figure 4: (patient 8) Axial and Coronal Ultra-Low Dose CT Thorax pretreatment (A) and 24 weeks post modified dose regimen(B)



DISCUSSION

➢This real-world data, and published work do date highlight;
- ✓ Some patients don't tolerate standard full dose of CFTR modulation therapy
- ✓The need in a small group to individualize dosage to minimize side-effects whilst continuing to safely clinically modulate.

➢Dose modification in our cohort resulted in;
- ✓Resolution of self-reported mental health adverse events
- ✓Sustained clinical effectiveness (comparable to full-dose)

➢Long term outcome of the reduced dose of ETI therapy is critical and ongoing.

➢Access to routine drug levels to compliment clinical /sweat chloride monitoring may be useful.

➢A limitation of this work is that the role out was during the covid-19 pandemic however the temporal relationship between drug initiation and symptoms make us feel that this would have happened independently of the pandemic.

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