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SHORT COMMUNICATION

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The complexities of elexacaftor/tezacaftor/ivacaftor therapeutic drug monitoring in a person with cystic fibrosis and *Mycobacterium abscessus* pulmonary disease

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ABSTRACT

Therapeutic drug monitoring (TDM) of elexacaftor/tezacaftor/ivacaftor (ETI) remains challenging due to a lack of clarity around the parameters that govern ETI plasma concentrations, whilst the use of concomitant CYP3A inducers rifabutin and rifampicin is not recommended. We present the complexities of TDM for ETI performed in a person with cystic fibrosis and refractory *Mycobacterium abscessus* pulmonary disease. Utilising National Association of Testing Authorities (NATA) accredited assays and target considerations published by the Therapeutic Goods Administration (TGA), Australia, ETI plasma concentration variability was monitored over the course of an acute admission with added complexity from an antibiotic regimen including rifabutin, a moderate cytochrome P450 3A (CYP3A) inducer, and clofazimine, a mild CYP3A inhibitor. This case highlights the challenges surrounding ETI TDM in the context of acute severe illness, malnutrition, chronic infection, and drug-to-drug interactions. The marked clinical improvement seen, alongside sustained ETI plasma concentrations and suppressed sweat chloride levels on serial testing, provided reassurance of the use of ETI and rifabutin concomitantly in this case, and highlights the potential utility of TDM in helping guide clinical practice. Though a current barrier to the application of TDM includes ETI only being available as a fixed dose combination.

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Short communication

The introduction of the transmembrane conductance regulator (CFTR) modulator elexacaftor/tezacaftor/ivacaftor (ETI) has transformed the management of eligible people with cystic fibrosis (CF). However, there remains a lack of understanding around the factors that govern the metabolism of ETI, particularly in the context of potential drug-to-drug interactions [1]. On this background, we undertook therapeutic drug monitoring (TDM) using accredited assays to evaluate the plasma concentrations of ETI in an adult person with CF (pwCF) receiving complex antibiotic treatment for *Mycobacterium abscessus* (Mabs), specifically analysing the combined impact on metabolism of ETI by rifabutin, a cytochrome P450 3A (CYP3A) inducer, and clofazimine, a CYP3A inhibitor [2]. This case highlights the complex treatment considerations encompassing inter-individual pharmacokinetic variability and drug-to-drug interactions when a CYP3A inducer and inhibitor are co-administered with ETI therapy. Signed consent was obtained from the pwCF to allow for his case to be described in this manuscript.

We describe the clinical application of ETI TDM in an 18-year-old pwCF (F508del/c.1646 G>A) established on standard dose ETI with refractory Mabs pulmonary disease. Following transition to adult care, his condition had been progressively declining with a nadir FEV1 of 33% predicted, associated with multiple admissions of escalating acuity. His latest presentation with a severe acute illness required intensive care (ICU) for non-invasive ventilation and subsequent high-flow nasal oxygen in the context of concurrent infection with rhinovirus, *Pseudomonas aeruginosa*, and Mabs. Treatment

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with anti-pseudomonal antibiotics was initially commenced before the focus of management changed to Mabs due to worsening clinical status. Given three previous failed attempts at Mabs eradication with guideline-based therapy over 10 years and a subsequent unfavourable resistance profile (minimal inhibitory concentrations (mg/L): cefoxitin 128; co-trimoxazole > 8; moxifloxacin > 8; doxycycline > 16; imipenem 64; linezolid > 32; clarithromycin > 16; amikacin 16), an induction regimen based on emerging *in vitro* data supporting the use of novel β-lactamase inhibitors was tailored consisting of intravenous (IV) ceftazidime/avibactam, imipenem/cilastatin, ampicillin, and amikacin [3]. His long-term oral azithromycin was also continued three times per week. Supplemental nutritional support via a nasogastric tube was commenced to meet his raised energy requirements. Given concerns about the absorption of ETI and possible increased renal excretion in the setting of critical illness secondary to sepsis [4], serial ETI plasma concentrations were assessed over a 12-h period following Mabs treatment commencement (Figure 1a). Although there are no clear targets for ETI TDM [1], it was felt appropriate to establish a baseline exposure to help guide future treatment and antibiotic regimen choice. TDM was undertaken at Pathology Queensland, Brisbane, Australia, using assays of ETI and its key constituent metabolites, developed and externally validated according to National Association of Testing Authorities (NATA) standards. The analytes of interest were assayed using an ultra-performance liquid chromatography tandem mass spectrometry method. In the concentration range from 0.01 to 20.0 mg/L, calibration curves were linear with a correlation coefficient >0.999 for all analytes. Rapid clinical improvement was seen following the introduction of Mabs directed therapy, with serial sputum cultures showing a transition from 2+ smear positive to smear negative within 2 weeks. ETI plasma levels were rechecked 2 weeks later, following stepdown from ICU (Figure 1b).

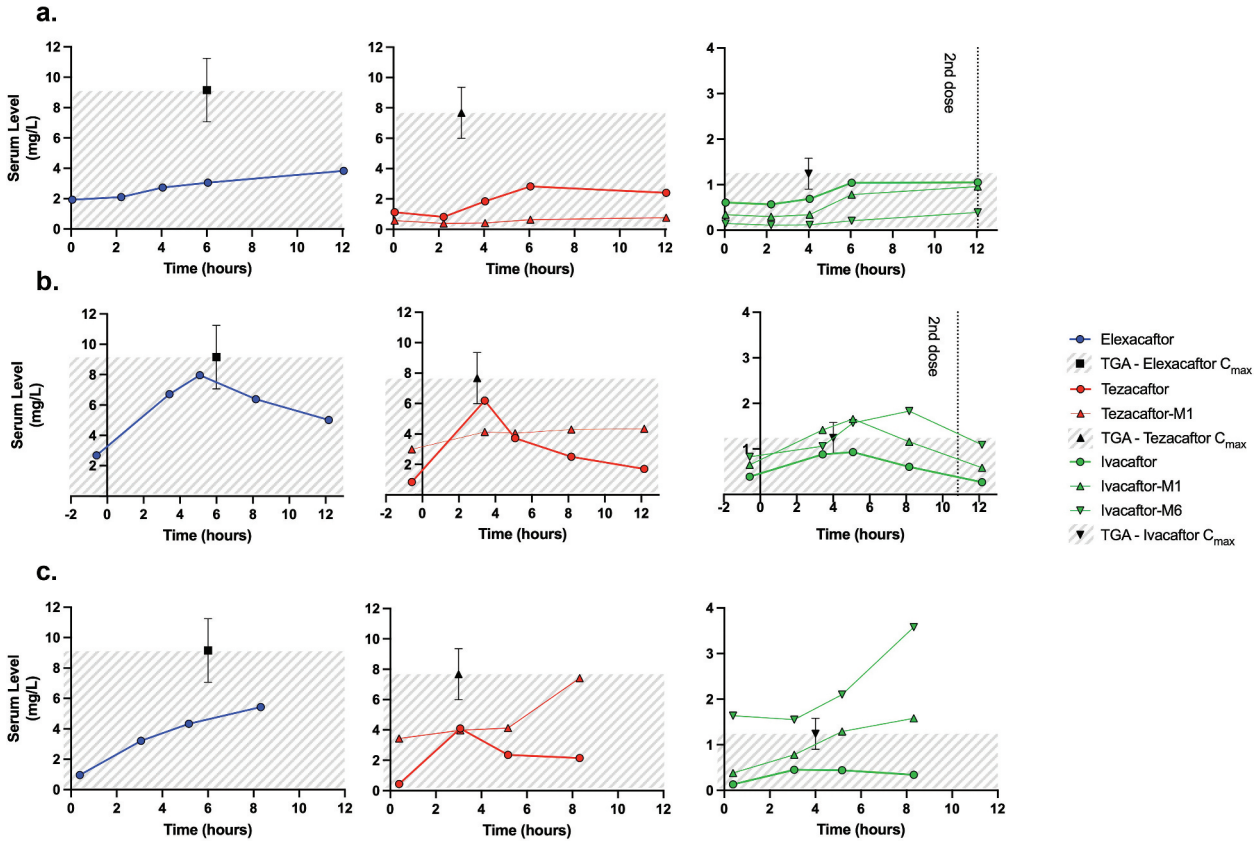

Figure 1. Serum levels of elexacaftor (blue), tezacaftor (red), and ivacaftor (green) with major associated metabolites. a: plasma concentrations collected over 12 hours in ICU immediately following commencement of IV antibiotics targeting Mabs, b: plasma concentrations collected over 12 hours following sustained clinical improvement 13 days after initiation of Mabs targeted therapy. Improvements in plasma concentration with peak levels for all constituent parts falling within one standard deviation of tga-published C_{max}, c: plasma concentrations collected over 8 hours, 6 days after initiation of rifabutin and clofazimine alongside IV antibiotic therapy. Concentrations of all three constituent parts are noted to have reduced, but increased metabolite levels are seen for tezacaftor-M1 and ivacaftor-M6. C_{max} values were obtained from TGA product information for ETI (mean ± standard deviation) [5].

The ongoing clinical improvement observed, combined with the rapid conversion to Mabs smear negativity, prompted a decision to extend IV therapy as a further attempt at eradication. Treatment duration was determined by recommendations from the current non-tuberculous mycobacterial pulmonary disease guidelines with a plan to administer IV antibiotic induction therapy for between 6 weeks and 3 months depending on aspects such as clinical response and antibiotic tolerability [5,6]. Treatment was consolidated with both rifabutin and clofazimine, not introduced earlier due to concerns about their potential interaction with ETI. Azithromycin was also increased to daily administration. Nutritional support was increased, corresponding with a BMI increase from 15.5 kg/m^2 to 19 kg/m^2 (Figure 2). Repeat ETI plasma concentrations were obtained 6 days after initiation of rifabutin and clofazimine (Figure 1c). IV amikacin was subsequently transitioned to amikacin liposome inhalation suspension (ALIS) [7,8].

There are three distinct pharmacokinetic (PK) patterns across the sampling times. Plasma concentrations of all components of ETI in ICU were below the C_{max} levels published by the Therapeutic Goods Administration (TGA), Australia (Figure 1a) [9]. Whilst wide variability in ETI plasma concentrations has been reported [10], the observed low levels possibly reflected a combination of poor absorption and/or increased renal excretion secondary to sepsis and critical illness, though evidence for this relating to ETI remains lacking. It is also possible that inconsistent adherence to treatment immediately prior to admission may have played a role. Poor adherence to ETI could theoretically have contributed to persistent Mabs infection, in contrast to other published experiences showing improvement of non-tuberculous mycobacterial infection with ETI [11–13].

Following the introduction of Mabs targeted therapy there was a rapid improvement in his clinical condition. Sputum smear negativity later correlated with culture conversion on five sequential sputum samples, the first negative mycobacterial culture results obtained in the last 10 years (Figure 2). Associated with this clinical improvement, increased plasma concentrations were noted for all three components of ETI. Peak levels had increased to within one standard deviation of the TGA published C_{max} values on stepdown from ICU and were felt likely to be within therapeutic range (Figure 1b) [9]. This improvement may reflect consistent ETI administration and an improvement in overall clinical status leading to increased absorption and/or reduced excretion. Certainly, a historical sweat chloride result from the first year of life, pre-*CFTR* modulator therapy, was elevated to 101 mmol/L. Repeat testing at the time of the second phase of ETI TDM was normal at 29 mmol/L and therefore felt to be consistent with a biological effect from ETI therapy.

Introduction of rifabutin and clofazimine raised concerns for CYP3A drug interactions with ETI [14,15]. The addition of rifabutin to the Mabs regimen was based on increasing interest in its use against Mabs and a lack of other viable oral alternatives in this case. This is based on *in vitro* analysis showing that rifabutin inhibits effective transcriptional induction of the *whiB7-erm41* system overcoming inducible macrolide resistance [16–18]. Following the introduction of both rifabutin and clofazimine, a reduction in plasma concentrations of all three components of ETI was

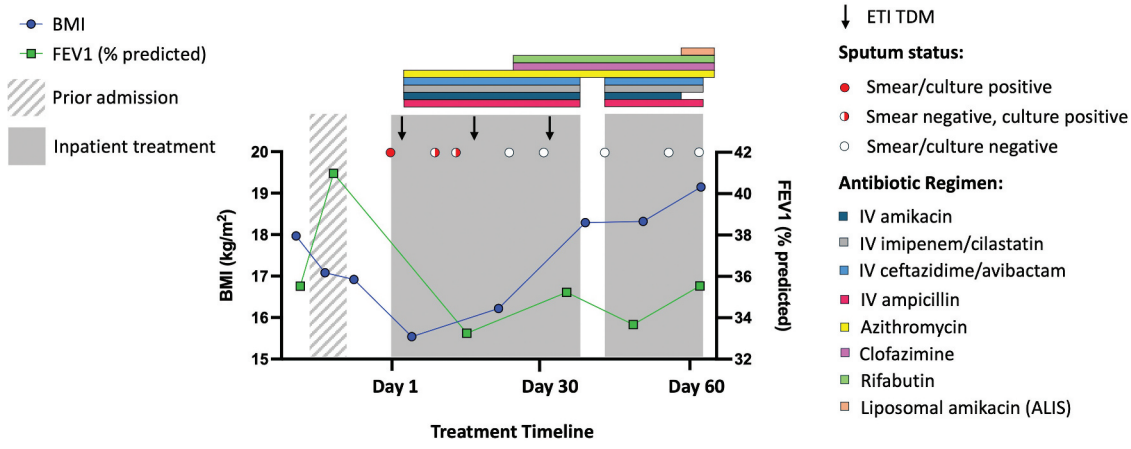

Figure 2. Disease trajectory over the course of treatment initiation for Mabs pulmonary disease. Clinical trajectory shown with BMI (blue), FEV1% predicted (green), sputum smear and culture status, time points of ETI TDM, and antibiotic regimen. Two separate inpatient stays are highlighted by the grey patterned areas. Sputum culture conversion represented the first negative mycobacterial culture results in 10 years.

observed. This was felt consistent with overall induction of CYP3A by rifabutin, which is a relatively 'stronger' inducer of CYP3A than clofazimine, which is an inhibitor (Figure 1c) [2]. However, while there has been a reduction in C_{max} values, ongoing drug metabolism is evident by the levels of clinically active metabolites tezacaftor-M1 and ivacaftor-M1. With ivacaftor-M6 being a clinically inactive metabolite. Clinical efficacy was therefore felt likely to be due in part to ongoing high levels of these clinically active metabolites. This was supported by a further normal sweat chloride result of 14 mmol/L taken whilst on both rifabutin and clofazimine. It is worth noting that, given its extended half-life, clofazimine levels are unlikely to have reached a systemic level at which significant CYP3A inhibition would be occurring by this time. Therefore, the impact of clofazimine may be greater in several months' time.

We provide further evaluation of the complexities of simultaneous CYP3A induction and inhibition on ETI plasma concentrations utilising accredited assays. ETI dose adjustments based on physiological simulation data have been previously suggested in the hypothetical setting of ETI co-administration with clofazimine or rifabutin individually, with subsequent case report data indicating sustained CFTR modulator benefit with concurrent rifabutin administration [2,19]. The impact of rifabutin and clofazimine on the plasma concentrations of the metabolites is worth considering further (Figure 3). Tezacaftor-M1 is documented as having a similar potency to tezacaftor, with ivacaftor-M1 exhibiting one-sixth of the potency of ivacaftor [9]. This could explain the maintenance of clinical stability from ETI alongside Mabs targeted antibiotic therapy. Additionally, the metabolite elexacaftor-M23, not analysed by our assays, is thought to exhibit similar potency to elexacaftor and may have increased in this scenario in a similar nature [9]. Ivacaftor exhibited comparatively smaller plasma concentration changes, except for the pharmacologically inactive ivacaftor-M6 metabolite [9].

While our data are reassuring, further understanding around ETI TDM is required. The availability of ETI TDM changed management in this case, as it allowed for the measurement of the impact of antibiotics with potentially significant drug-to-drug interactions on ETI serum levels and efficacy. The broader application of TDM may be limited because ETI is currently only available in fixed dose combinations, making individual drug dose adjustments challenging. There may be a role for isolated TDM in complex clinical scenarios such as in our case, but wider application of ETI TDM requires a greater understanding of the factors that govern ETI pharmacokinetics and pharmacodynamics including nutritional status, potential malabsorption, and individual variances in the CYP3A system due to genetic polymorphisms that may be encountered in CF [20]. Optimised sampling times for ETI PK evaluation, as well as uncertainty around therapeutic target ranges for ETI C_{max} and AUC, remain unclear and should be considered when

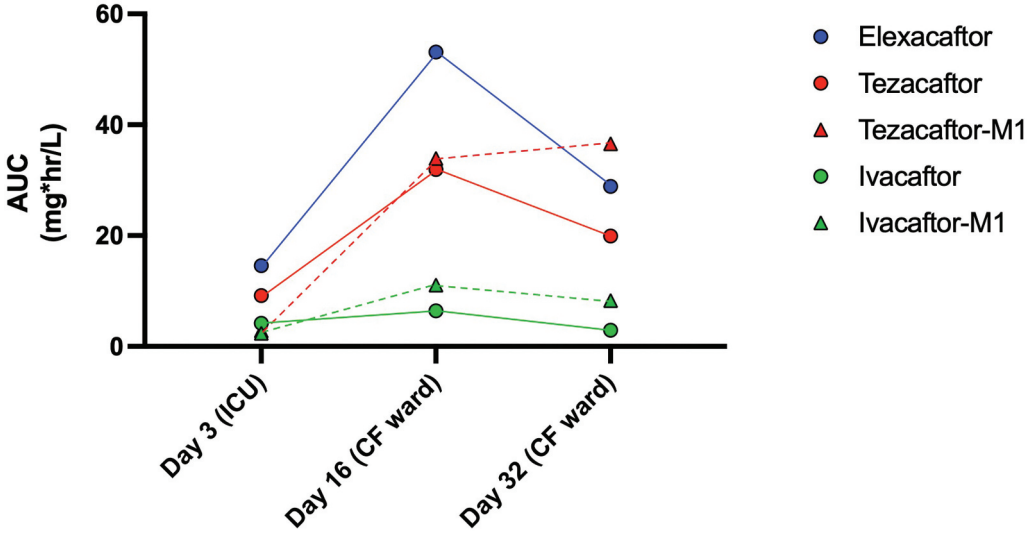

Figure 3. Area under the curve (AUC) across three time points of ETI TDM with levels taken on day 3 of admission (ICU), following improvement in clinical condition on day 16, and following initiation of rifabutin and clofazimine on day 32. While the AUC have reduced following initiation of rifabutin and clofazimine, they remain higher than compared to the levels taken in ICU. Additionally, levels of therapeutically active metabolites, particularly tezacaftor-M1, remain elevated. Calculated using GraphPad prism 10.2.3.

interpreting our data. Recently published data also suggests using ETI C_{min} to monitor drug exposure [21]. Our findings help to provide further insights into the complexities faced with ETI dosing and combination pharmacotherapy.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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