'Therapeutic drug monitoring-guided dosing for pediatric cystic fibrosis patients: recent advances and future outlooks'

Siân Bentley [1], Jamie Cheong[1], Nikesh Gudka[2], Sukeshi Makhecha[1], Simone Hadjisymeou-Andreou[3], Joseph F Standing[2,4]

1 Pharmacy Department, Royal Brompton Hospital, London, UK

2 Pharmacy Department, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

3 Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, UK

4 Infection, Immunity and Inflammation, Great Ormond Street Institute of Child Health, University College London, London, UK

Address for correspondence: Siân Bentley, Pharmacy Department, Royal Brompton Hospital, Sydney Street, London, SW3 6NP

Tel: +44(0)207 3528121 Email: s.bentley@rbht.nhs.uk

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Abstract

Medicine use in children with cystic fibrosis (CF) is complicated by inconsistent pharmacokinetics at variance with the general population, a lack of research into this and its effects on clinical outcomes. In the absence of established dose regimens therapeutic drug monitoring (TDM) is a clinically relevant tool to optimise drug exposure and maximise therapeutic effect by the bedside. In clinical practice though, use of this is variable and limited by a lack of expert recommendations.

We aimed to review the use of TDM in children with CF to summarise recent developments, current recommendations and opportunities for future directions. We searched PubMed for relevant publications using the broad search terms “cystic fibrosis” in combination with the specific terms “therapeutic drug monitoring (TDM)” and “children”. Further searches were undertaken using the name of identified drugs combined with the term “TDM”.

Further research into the use of Bayesian Forecasting and the relationship between exposure and response, is required to personalise dosing, with the opportunity for the development of expert recommendations in children with CF. Use of non-invasive methods of TDM has the potential to improve accessibility to TDM in this cohort.

Keywords: Antimicrobials; Children; Cystic Fibrosis; Cystic Fibrosis Transmembrane Regulator (CFTR); Pharmacokinetics; Therapeutic Drug Monitoring

Introduction

Cystic fibrosis (CF) is a life threatening autosomal–recessive disorder with an incidence of approximately one in 2,500 in the UK(1). CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Although a multisystem disorder, lung disease is the major cause of morbidity and mortality. CFTR dysfunction leads to a defect in chloride secretion and a loss of inhibition of airway epithelial sodium channels which, in turn, leads to dehydration of airway surface liquid. Thus, the lungs are not able to effectively clear inhaled organisms due to impaired muco-ciliary clearance(2). The lungs of children with CF appear normal at birth, but quickly become infected by microorganisms. This often results in a progressive decline of lung function with intermittent episodes of acute worsening of symptoms, called 'pulmonary exacerbations'(3).

People with CF experience multiple exacerbations throughout life, however the bacterial flora in the lungs can change over time, with some pathogens being more virulent than others(1). *S.aureus, H.influenzae* and *S.pneumoniae* are the bacteria most often encountered in exacerbations in infancy and early childhood(4). From mid-childhood onwards *P.aeruginosa* is the predominant bacterial pathogen(1). Early infection is readily eradicated if treated aggressively. However, recurrence is common and chronic infection results in a more rapid decline in lung health in relation to the organisms resilience to host immune defence mechanisms(5-7). Fungal infection, commonly *A.fumigatus,* is also associated with poor lung health as it can be difficult to detect. This can cause significant lung disease (fungal bronchitis; saprophytic; invasive; or allergic (allergic bronchopulmonary aspergillosis (ABPA)(8). Early, timely and optimal treatment of pulmonary exacerbations is critical in improving the quality and length of life.

Most recently, disease-modifying drugs that specifically target the consequences of CFTR gene variants have become available. Huge benefits have been seen in those eligible for these medicines including improvements in lung function and a reduction in exacerbations(9). However despite these positive outcomes there is still limited real world data available on their effect on clinical outcomes(10).

Due to developmental changes occurring throughout childhood, the pharmacokinetics (PK) and pharmacodynamics (PD) of medicines used in children differ to adults. These differences can affect drug levels, treatment response and potential for toxicity/ adverse effects, and differ throughout the age range(11). This can be further complicated by a lack of biomarkers and /or disease progression measures suitable for use in children(12). However, paediatric studies underpinning these concepts are lacking, and therefore dose recommendations for children are often extrapolated from adults without due consideration to these issues(13).

When considering how we can optimise therapies for children with CF there is a further conundrum to reflect on – people with CF display altered pharmacokinetics for some drugs as a consequence of co-morbidities affecting drug absorption and disposition(14, 15). Changes within the gastrointestinal tract such as pancreatic insufficiency and bile acid dysfunction may result in slower and/or reduced extent of oral absorption, leading to lower overall drug exposure (AUC) or peak drug levels (C_{max}). It is postulated that the lower adipose tissue to body weight ratio, decreased serum levels of albumin, augmented GFR, and inflammatory modulation of drug metabolism, may be responsible for changes in drug disposition, leading to increased clearance (CL) and volume of distribution (Vd)(14, 15).

With a lack of concrete information on which to base recommendations for dosing regimens for children with CF, the use of therapeutic drug monitoring (TDM) is one of the most clinically relevant tools available, with the aim of optimising drug exposure and maximising therapeutic effect. Drugs where TDM is most useful are those that show substantial inter-individual PK variability which may not be predictable from patients characteristics, and a correlation between concentration and response (both efficacy and toxicity)(16).

We aimed to review the use of TDM for drugs used in children with CF, to summarise recent developments, current recommendations, and opportunities for future development in this area. Where there is no relevant data in children with CF, we have included data in adults with CF. We searched PubMed for relevant publications using the search terms “cystic fibrosis” in combination with the terms “therapeutic drug monitoring (TDM)” and “children”. Further searches were

undertaken using the name of identified drugs combined with the term "TDM". Reference lists of each selected publication were also reviewed to identify further relevant publications

1. Antibiotics

Traditionally TDM has been carried out on antimicrobials with a low therapeutic index which have high association of toxicity(17). Trough (pre-dose) level monitoring is taken as close to before the next dose and measures the lowest level of drug in the body (C_{min}). For drugs such as aminoglycosides C_{min} is used to minimise toxicity by avoiding accumulation, and for drugs such as glycopeptides serves a dual purpose of maximising efficacy and minimising toxicity(18, 19). Peak levels are taken to detect the maximum drug levels in the body (C_{max}) and are done to ensure levels are within the therapeutic range. However, with the global threat of increasing antimicrobial resistance and limited number of antimicrobials available, TDM increasingly considers the minimum inhibitory concentration (MIC) of an organism. This takes into account the PK/PD profiles of antimicrobials, often described as time dependant (relates to the time that the antimicrobial concentration is above the MIC [T>MIC]) or concentration dependent (relates to the peak concentration above the MIC [C_{max}/MIC]); or both where area under the curve to MIC ratio (AUC/MIC) is the most effective measure(20).

1.1 Aminoglycosides

Aminoglycoside antibiotics form the main stay of antimicrobial management of infections in children with CF. They are used to treat a broad range of organisms such is *P.aeruginosa*, MRSA, *M.abcessus* and *B.cepacia* complex(21). Aminoglycosides exhibit bactericidal concentration dependent killing by disrupting protein synthesis by binding to the 30S ribosomal subunit causing inaccurate translation of mRNA(22). They also take advantage of concentration-dependent post antibiotic effect (PAE) where, despite the serum concentrations fall below MIC, drug efficacy is not compromised because PAE prevents bacterial re-growth. PAE represents the time it takes for ribosomal protein to be re-synthesised(23).

TDM is essential for aminoglycosides utilising an approach that maximises efficacy – both C_{max}/MIC ratio and AUC_{24}/MIC have been utilised as PK/PD parameters(24); and trough levels (C_{min}) are low enough to minimise toxicity(19). The main side effects that are of concern with aminoglycoside use, include ototoxicity and nephrotoxicity, which can lead to irreversible loss of function. It is estimated that >50% of people with CF will experience hearing loss before they reach adulthood and 80% of those receiving more than 10 courses of aminoglycosides will have permanent hearing loss(25). Pharmacokinetic modelling was used to predict the risk of ototoxicity with intravenous tobramycin in 38 people with CF (8 – 21 years)(25). Their results yielded those patients with more severe hearing loss were older and had higher trough concentrations >2mg/L, reinforcing the need for TDM.

Traditionally TDM for aminoglycosides in all people with CF has focussed on measurement of trough concentrations and peak concentrations to ascertain safety and efficacy respectively(26, 27). This method is still used by many centres, likely due to the ease of measurement and interpretation, and was utilised in the TOPIC multicentre study, evaluating the clinical outcomes in people with CF, including children, of once daily versus thrice daily tobramycin(28). Target concentrations of tobramycin for the once daily regimen were trough concentrations of $\leq$1mg/L and peak concentrations of 20–30 mg/L. The primary endpoint was a mean change in FEV_1 % predicted, and once daily dosing resulted in a mean change in FEV_1 (% predicted) over 14 days of 10·4%. Conversely, the use of alternative TDM methods encompassing the PK/PD target AUC_{24}/MIC have been used for many years in some regions including Australia(29). Mouton et al demonstrated a significant relationship between C_{max}/MIC and AUC_{24}/MIC of tobramycin and efficacy parameters (increase in FEV_1 and FVC) in children and young adults with CF(30).

More sophisticated TDM methods have evolved to measure AUC_{24}/MIC, with a particular focus on individualised dosing. Log-Linear Regression (LLR) method utilises tobramycin levels taken at two specific time points, assumes a one-compartment intravenous infusion model, and uses a Microsoft excel spreadsheet embedded with relevant equations to calculate AUC_{24}(31). Bayesian forecasting (BF) methods use population derived pharmacokinetics combined with patient's dosing history,

demographic data and a single tobramycin level at any time point inputted into programmes to estimate AUC_{24} and adjust dosing(31). Burgard et al used 3 available BF programmes (TDMx, InsightRX and DoseME) and LLR method to compare AUC_{24} in 55 children with CF(31). All three BF programs estimated statistically significant ($p \leq 0.01$) higher AUC_{24} (TDMx 92.5 [81.3–105.3] mg/h/l^{-1}, InsightRX 96.0 [82.0–108.0] mg/h/l^{-1}, DoseMe 92.9 [81.1 to 105.0] mg/h/l^{-1}) compared to LLR method 89.2 [74.3–102.1] mg.h.l^{-1} for an AUC target of 100 mg/h/L^{-1}. This correlates with dosing data where LLR predicted higher doses 10.6 [8.4 to 13.3] mg/kg due to lower AUC_{24} versus TDMx 10.0 [8.3 to 12.0] mg/kg, InsightRX 9.8 [7.9 to 11.9] mg/kg and DoseMe 9.8 [8.1 to 12.0] mg/kg. The authors commented that despite the availability of technology to use AUC to calculate individual doses, the practice is not widely adopted, and more research is needed. Recently, a quasi-experimental pre-post intervention study evaluated LLR and BF methods in 378 admissions in children with CF(32). Precision dosing was defined as tobramycin $AUC_{0\text{-}24}$ within a range of 100–110mg/l/h. Children monitored with the LLR method had twice the number of serum samples per single hospital admission (LLR = 3.8 versus BF = 1.9; $P < 0.001$). The median tobramycin dose prescribed was higher where BF was used compared with LLR, during both initial (430 versus 390mg; p=0.18) and maintenance (400 versus 395 mg; p=0.89) therapy. A change from the empirical dose was more frequently observed in the BF group (72%; 92/128) compared with the LLR group (63%; 155/248) although not statistically significant (p=0.07). The mean tobramycin $AUC_{0–24}$ was higher in the BF group both when the first (BF = 106mg/L/h versus LLR = 94.7mg/L/h; $P < 0.001$) and final (BF = 102.6mg/L/h versus LLR = 95.1 mg/L/h; $P <0.001$) and the target $AUC_{0\text{-}24}$ of $\geq$100mg.l/h was achieved more frequently in the BF group (72%; 92/128) versus the LLR group (50%; 124/248) ($P < 0.001$). A higher proportion of the BF group (39%; 50/128) achieved $AUC_{0\text{-}24}$ precision range compared to the LLR group (25%; 61/248) (P=0.004). The authors concluded that both the LLR and BF method predicted tobramycin $AUC_{0\text{-}24}$ with similar accuracy. BF lead to less blood tests, a higher likelihood of achieving target concentrations (BF 72% versus LLR 50%) and greater precision of target attained, compared to the LLR method (BF 39% versus LLR 25%). Prospective studies are needed to validate these findings.

Though the need for TDM for aminoglycosides in children with CF is well established, many centres only carry out trough monitoring in children with CF routinely(29). Reasons for this include the costs and practicality of repeated blood tests, in addition to an assurance that the doses used were sufficient to reach the PD target and clinical endpoint for a majority of patients(24, 28). However, if we are to individualise each patient episode and maximise effectiveness by achieving favourable AUC_{24}/MIC or C_{max}/MIC then levels throughout the dosing interval are a necessary part of TDM for aminoglycosides. With the use of sophisticated BF methodologies and associated software this is becoming a realistic widespread approach.

1.2 Beta-lactams

T>MIC is the best predictor of efficacy for B-lactams(33). For beta-lactams 40% is assumed, but for maximum effect it is recommended that the targeted T>MIC should be 60%-70% of the dosing interval for cephalosporins for most pathogens(34) 40% for carbapenems and 50-60% for penicillins and monobactams(35, 36).

PK studies have shown that clearance of both ceftazidime and meropenem is higher in children with CF compared to those without, therefore higher or more frequent dosing is required(37-39). Ceftazidime intermittent 30-minute infusions achieve a T>MIC 60-70% in children with CF if *Pseudomonas aeruginosa* MIC<8mg/L using higher doses of ≥50mg/kg TDS, compared to non-CF children who can attain this target at higher doses when MIC are ≤16mg/L(37). To reach the recommended T>MIC (65%) for ceftazidime and meropenem (40%) short intermittent infusions need to be changed to 3 hour extended infusions when MIC ≥8mcg/L for ceftazidime(37) or MIC≥4mg/ml for meropenem(38). Conversely the use of ceftazidime as a continuous infusion achieves the PK/PD target for all children, with and without CF, even at MIC 16mg/L(37). Of note B-lactam clearance (ceftazidime, meropenem, aztreonam, piperacillin/tazobactam, ticarcillin/clavulanate) has also been shown to increase between days 2 and 7 in adults with CF receiving continuous infusions necessitating a 20% increase in B-lactam dose in approximately 50% of patients(40).

Although T>MIC 40% is the suggested PK/PD target for meropenem, achieving 65% fT>MIC was shown to be a significant predictor of response when using extended infusions of meropenem in children with CF with acute pulmonary exacerbations. This showed a relative improvement in FEV_1 % predicted of at least 15%(41). A randomised controlled trial demonstrated significant improvement in FEV_1 % predicted in both adult and children with CF when using ceftazidime continuous infusions compared to intermittent infusions for resistant strains of *Pseudomonas aeruginosa* (MIC>32mg/L)(42). Mean ceftazidime levels were 56.2+/-23.2mcg/ml for continuous infusions, whilst peak levels were 216.3+/-71.5mcg/ml and trough levels were 12.1+/-8.7mcg/ml for 30-minute intermittent infusions. In adult CF patients, using TDM for piperacillin/tazobactam and cefepime has been shown to reduce the frequency of exacerbations from 1.91 to 1.31 exacerbations/year, with longer intervals between exacerbations (103.7 days to 196.2 days) and a slower decline in FEV_1 % predicted (-9.7 (pre-TDM) vs -4.9 (post-TDM)(43).

In individual circumstances TDM has been useful to guide antibiotic dosing when using multiple antibiotic combinations (aztreonam and ceftazidime/avibactam) to achieve a reduced MIC (from ≥256mcg/ml for individual antibiotics down to 8mcg/ml when used in combination) in a paediatric CF patient with resistant *Stenotrophomonas maltophilia*(44). Drug levels were taken at steady state: for intermittent infusions this was immediately after the end of the infusion and 1 hour after the end of the infusion; for continuous infusions this was after a minimum of 8 hours. Based on TDM, a dose increase and change to continuous infusion with ceftazidime led to 100% T>MIC being achieved for both aztreonam and ceftazidime. Despite clinical improvement and achieving target PK/PD parameters, lung function did not recover, highlighting that although TDM is useful it should be used in conjunction with other clinical investigations.

Where there are altered PK profiles such as in a critically ill CF adult on ITU and ECMO with augmented renal clearance leading to low trough levels of meropenem, a switch to continuous infusion of the same daily dose of 6g/day ensured that target levels were reached (17.3-23.2mg/L)(45). When the same patient received transplanted lungs colonised with *Acinetobacter baumannii* with MIC=32mg/L

the dose was increased to 8g/day given as a continuous infusion over 12 days to attain levels above the MIC at 39.6mg/L. They were also administered IV sulbactam, tigecycline with inhaled colistin and the patient was discharged from ITU without signs of infection. Positive outcomes were also achieved in an adult CF patient treated with ceftazidime/avibactam 2.5g every 8 hours and trimethoprim/sulfamethoxazole for *Burkholderia cepacia* colonisation(46). TDM showed ceftazidime trough levels were maintained above the MIC (2mg/L) and patient was discharged from the ward after 2 weeks with surveillance cultures 1 month later reporting that the MIC remained unchanged. Adequate drug levels ensured minimal emergence of resistant strains.

The increased clearance seen in people with CF leading to lower T>MIC with B-lactams necessitating higher dosing or the conversion to extended/continuous infusions, particularly in organisms with a higher MIC, would seem to justify the use of TDM. However instability of B-lactams in clinical samples requires them to be processed within a short time frame or adequately stored at the correct temperature(47). Rapid degradation occurs within 4 hours leading to inaccurately low levels and erroneous PK parameters which could then be used to miscalculate changes in drug dosing(48). Due to the need for additional information e.g., MIC of targeted organism, as well as a PK/PD software package to calculate target T>MIC, the need for frequent sampling (peak, trough, steady state, drug levels at set time intervals) and potential drug costs if dose increases are required, TDM of B-lactams may be associated with increased costs. Additionally, there is a paucity of evidence in children with CF and further studies are needed before recommending this in routine clinical practice. Nevertheless, TDM could be a useful adjuvant for optimising B-lactam dosing for children with CF where drug levels are affected due to changes in PK (increased CL, increased Vd in critically ill patients, organ dysfunction); where there are drug interactions; in the presence of resistant organisms to ensure target T>MIC; and to minimise the development of antibiotic resistance.

1.3 Vancomycin

Glycopeptides have a broad spectrum of activity against gram positive bacteria, including MRSA infections, which have become common in people with CF and associated with a decline in pulmonary

function(21, 49). However it has poor penetration into the lungs(49), can cause renal impairment, drug reactions with eosinophilia and systemic symptoms and has a low therapeutic index with a recognised requirement for TDM.

Historical practice for TDM of vancomycin (though not specific to CF) recommended that AUC/MIC ≥400 was the best predictive pharmacokinetic parameter to attain clinical effectiveness, and that trough levels of 10 – 20 μg/ml, as a surrogate marker, was the most accurate and practical way to attain this.(26, 50, 51). However, updated vancomycin guidelines for MRSA infections have changed their recommendation to achieve a target AUC/MIC ratio 400-600 (assuming vancomycin MIC 1mg/L) to maximise efficacy and safety by individualised AUC guided dosing using first-order PK equations or Bayesian software programs following 1-2 samples (usually 1 peak and 1 trough level) achieved within 24-48 hours of initiation for early appropriate treatment(18). Trough-only monitoring is no longer recommended. Indeed, a retrospective cohort study in 30 children with CF with MRSA treated with vancomycin found that trough concentrations did not correlate with either AUC or AUC/MIC(52). Although, there was a strong positive correlation between the vancomycin dose and AUC and AUC/MIC.

A study evaluating the precision and bias in estimating the AUC of vancomycin using TDM (aiming for a target of AUC/MIC $\geq$400) in 23 children with CF obtained using either population PK models from a single trough concentration or 2 point estimated AUC monitoring using standard pharmacokinetic equations found that there was no significant difference between the models used (p=0.89) and that both models were unbiased and precise(53). It should also be noted though that to date there is no evidence to show that AUC based TDM correlates with clinical efficacy in children with CF(53). Mitchell et al compared the occurrence of acute kidney injury (AKI) in adults and children with CF receiving vancomycin and undergoing TDM using either single trough concentrations or 2 point estimated AUC monitoring using the Sawchuk–Zaske equation(54). Target concentrations were trough levels 10-20 mg/L or latterly AUC 400–600 mg.h/L. The secondary objectives were time to return to baseline lung function and time to next pulmonary exacerbation. The study found that there was a significant

difference in the number of adults that returned to within 10% of their baseline lung function in the AUC monitoring group (p=0.002). Though not statistically significant the reverse was found for children with 80% of those monitored via trough levels returning to baseline lung function whilst 67% of those monitored via AUC returned to baseline lung function (p = 0.458). There was no statistically significant difference in the occurrence of AKI in either children or adults, all grade 2–3 AKI's in adults were in the single trough level group, which may be as a result of lower daily doses observed in the AUC group.

Individualised AUC guided dosing, already adopted by many centres managing children with CF, has the potential to improve clinical outcomes and reduce toxicities associated with vancomycin therapy. With the potential shown by models utilising one trough concentration, which minimises the need for multiple blood samples, the stumbling block may be access to technology and / or expertise to carry out complex modelling. Though simpler to implement, 2-point AUC monitoring relies on two blood samples. However, there is a need for further research to establish whether AUC based TDM for vancomycin correlates with clinical efficacy in children with CF, and an opportunity to further investigate the applicability of the most recent recommendations using individualised AUC guided dosing for children with CF(26, 50).

2. Antifungals

In people with CF triazole antifungals are commonly used to treat infection caused by *A.fumigatus*, Scedosporium species and *E.dermatitidis*, or manage Allergic Bronchopulmonary Aspergillosis (ABPA), an inflammatory condition of the lungs precipitated by the presence of *A.fumigatus* in the airways. Triazoles exert their action by inhibiting 14α-demethylase which catalyses the synthesis of ergosterol from lanosterol, thereby disrupting the cell membrane of the fungus and causing cell death(55).

2.1 Itraconazole

Itraconazole is the triazole that has been in clinical use for longest with oral formulations most commonly used for treatment of Aspergillus and ABPA in children with CF(56, 57).

Itraconazole exhibits marked inter individual variability in pharmacokinetics in children with CF(56, 58, 59), which may be due to the multiple factors in children with CF that can affect the absorption of lipophilic drugs such as itraconazole, including exocrine pancreatic insufficiency(55). Many children with CF also require concomitant H_2 antagonists and proton pump inhibitors to manage gastro-oesophageal reflux which can affect the bioavailability of the capsule formulation, which requires an acidic environment for dissolution(55). In a number of studies in which itraconazole TDM was carried out, children with CF have failed to meet the therapeutic thresholds as defined by the studies(56-58, 60). Most recently a retrospective, case control, single centre study in children and adults with CF investigating the use of prednisolone and itraconazole for the treatment of ABPA, in which itraconazole TDM was carried out, identified that patients with lower itraconazole serum trough levels during the first 3 months of treatment subsequently faced a relapsing disease course, suggesting that dose optimisation may confer clinical benefits(61). This relationship between serum concentrations and treatment efficacy, alongside the high inter-individual variability seen in itraconazole concentrations in children with CF lends weight to the argument for TDM. The ability to carry out TDM is also of practical use since itraconazole undergoes oxidative metabolism via the via CYP3A4 pathway in the liver, and is therefore subject to numerous drug-drug interactions (DDI) with medicines that share this pathway or alter the function of the CYP3A4 enzyme, leading to increased or reduced itraconazole serum concentrations(55, 62).

Due to a paucity of data around the PK/PD relationships of triazoles for CF fungal lung disease, recommendations for TDM are extrapolated from other populations including adults and for invasive disease(63). ESCMID-ECMM guidelines for the treatment of invasive aspergillosis in neonates and children state that a trough level of 1-4 mg/L (itraconazole plus hydroxy-itraconazole) should be achieved using HPLC(64). If measuring using bioassay, a range of 5–15 mg/L is usually recommended(57, 65). To note a standard trough concentration does not incorporate the MIC of the fungal pathogen, and so greater exposure may be required to maximise outcomes for organisms with a higher MIC, which would not be reflected in the trough concentration target.

2.2 Voriconazole

Voriconazole, a second generation triazole, has a similar spectrum of activity to itraconazole(21) and has been in clinical use for children with CF since 2002 when it was used as a therapeutic alternative to itraconazole(66). Similarly to itraconazole voriconazole is subject to numerous DDI's due to its metabolism via CYP2C19(65), which is further complicated by genetic polymorphisms in this pathway, which can lead to variations in the metabolism of medicines that utilise this pathway, for example poor or extensive metabolisers(67).

Voriconazole is associated with numerous adverse effects, including liver toxicity, ocular effects and squamous cell carcinoma(68). A meta-analysis investigating the utility of voriconazole TDM found that there was a statistically significant link between high voriconazole levels (as defined by the included studies) and toxic effects which included hepatotoxicity, gastrointestinal intolerance, and neurotoxicity ($P<0.001$)(69). This meta-analysis did not include adults or children with CF due to paucity of literature available at the time of review, however Markantonis et al investigated the relationship between voriconazole levels and photosensitivity in children with CF. They found no correlation between voriconazole serum concentrations and photosensitivity in 6/8 children who experienced a phototoxic rection(70). Of the liver function tests measured they found that GGT levels were associated with voriconazole levels (C_{max} $p=0.0374$ and C_{min} $p<0.0001$), and in one child they reported that after reducing the dose of voriconazole an improvement in hepatic function was seen. This study also described high inter-individual variability in both C_{max} and AUC, although this was put partially down to the use of fixed doses as opposed to per body weight with significant correlations between the doses received and C_{max} ($p=0.0037$) and estimated AUC ($p=0.0015$). Trough concentrations were found to be <1 mg/L in 8/10 of children included. They also determined the CYP2C19 genotype in their patients, and one patient with a poor metaboliser genotype was found to have the highest C_{max} and AUC values of the series. An inability to reach therapeutic drug concentrations with standard doses was also demonstrated in a case series examining the use of TDM

for itraconazole and voriconazole in children with CF, in which only 2/8 children reached therapeutic voriconazole trough concentrations (aiming for 1.3–5.7mg/L), and 1 child had undetectable levels(57).

Like itraconazole there is a lack of pharmacodynamic data on which to base specific recommendations for children with CF in relation to clinical outcomes. However, we know that in other populations patients with therapeutic voriconazole serum concentrations are twice as likely to achieve successful outcomes(69). ESCMID-ECMM guidelines for the treatment of invasive aspergillosis in neonates and children state that a trough level of 1-5.5 mg/L is recommended, though suggests a higher level of 2–6 mg/L for infections caused by Aspergillus spp. that have an MIC of $\geq$2 mg/L(64). Given the high inter-individual variability seen in the available data on voriconazole in children with CF, as well as the potential for DDI's and the possible impact of CYP2C19 genetic polymorphisms there is a clear need to measure serum concentrations both to prevent toxicity and maximise outcomes.

2.3 Posaconazole

Posaconazole is structurally similar to itraconazole, and is becoming the agent of choice, due to the poor tolerability and toxicity of the other triazoles(71). It is metabolised via UDP glucuronidation and is a substrate for p-glycoprotein efflux(72). Posaconazole itself is a potent inhibitor of CYP3A4 which, in keeping with the other azoles, means that DDIs are common(72).

Data on the use of posaconazole in children with CF is limited to case reports and case series(73-78). A number of these have demonstrated with TDM that therapeutic concentrations of >1mg/L are readily attained in children with CF(73, 74, 76). A prospective observational study included 14 children with CF and reported that posaconazole trough concentrations of >1 mg/l were achieved in all children ($\geq$ 12 years old) receiving posaconazole tablets at a dose of 300mg OD, although only 60% of children attained therapeutic concentrations whilst receiving posaconazole oral suspension(73). Bentley et al described the use of posaconazole tablets, in combination with terbinafine to treat Scedosporium species in 5 children with CF(76). Posaconazole concentrations were >1mg/L in all children. A population pharmacokinetic study of posaconazole tablets in children with CF demonstrated that the

pharmacokinetics of posaconazole in children with CF were in line with children without CF, as established by Boosathorn et al(71, 79). Of note was the high inter-individual variability in clearance.

In the absence of information linking a posaconazole TDM target with clinical outcomes in children with CF, a target of >1 mg/L is generally accepted(64). Though not validated in children with CF, Patel et al found that using this TDM target concentration children treated with posaconazole showed improvements in lung function(73). However, dosing simulations carried out against the trough of 1mg/L, as well as an alternative target of AUC of 30mg/L - found to be associated with improved clinical outcomes in adults with invasive aspergillosis(71, 80) - found the AUC target to correlate with a trough target of 0.75mg/L. Further work is required to ascertain if this is sufficient to optimise outcomes in children with CF.

Given the paucity of data linking the pharmacokinetics and pharmacodynamics of posaconazole in children as well the inevitable inter-individual variability and DDI's, TDM is necessary to maximise therapy in this cohort. It should be noted however that availability of antifungal assays might be limited to specialist centres increasing the time and cost for routine TDM and thereby limiting their clinical utility(65).

3. Ibuprofen

Ibuprofen has been used for many years in people with CF as an anti-inflammatory therapy and has been shown to slow the rate of decline in FEV_1, more notably so in children(81-84).

TDM is recommended in children with CF on high dose ibuprofen therapy to determine dose requirements at initiation, periodically during maintenance therapy to assure optimal dosing requirements, and to redefine dosing if clinical circumstances change, for example, with significant weight changes(85, 86). TDM consists of a 3 hour pharmacokinetic study with determination of peak ibuprofen levels measured by high-performance liquid chromatography every 60 minutes after the administration of ibuprofen (20 to 30 mg per kilogram of body weight, to a maximum of 1600 mg) for 3 hours(81, 85). Doses are adjusted to a target ibuprofen plasma concentrations of 50 - 100

micrograms/mL, with levels greater than 50 micrograms/mL shown to inhibit neutrophil migration, and levels less than 50 micrograms/mL leading to an increase in neutrophil influx to mucosal surfaces and higher neutrophil counts(87). Levels greater than 100 micrograms/mL are associated with increased adverse effects(85).

Recognition of the need for TDM arises from inter-individual variability in the pharmacokinetics in children with CF(88), pharmacokinetic differences between formulations(89), together with the potentially detrimental association between subtherapeutic levels of ibuprofen <50 micrograms/ml and pro-inflammatory effects(86, 87). Most recently, published data highlighted a DDI between lumacaftor/ ivacaftor and ibuprofen as a result of CYP450 enzyme induction by lumacaftor, highlighting further potential for variability in levels(90). However, concern has been raised about the challenges of carrying out the pharmacokinetic dose finding studies required for initiation of therapy(91), and facilities to process levels may not be widely available outside regions where this therapy is used widely. Alternative methods to carry out dose optimisation for ibuprofen would be welcomed.

4. CFTR modulators

CFTR modulators are small molecules specifically targeting the consequences of CFTR gene mutations. Currently available CFTR modulator compounds fall into two categories known as potentiators and correctors(92). Potentiators (ivacaftor), facilitate increased anion transport by potentiating the channel-open probability of the CFTR protein at the cell surface(92). Correctors (lumacaftor, tezacaftor and elexacaftor) facilitate increased anion transport by correcting misfolding errors and increasing the quantity of protein delivered to the cell surface and are used in combination with potentiators (ivacaftor/lumacaftor, ivacaftor/texacaftor, elexacaftor/tezacaftor/ivacaftor) to synergistically enhance anion transport of F508del-CFTR protein via the two different mechanisms(92).

TDM is not currently used for CFTR modulators in routine clinical practice, however there is debate about its clinical utility (16), since following their introduction, it has become clear that there is still much to learn about their PK/PD in a real-world setting.

High inter-individual variability in the plasma levels of ivacaftor and lumacaftor/ivacaftor has been described(93-96). This variability is further compounded by numerous DDI's since they are primarily metabolised in the liver via cytochrome P450 (CYP450) enzymes, specifically CYP3A4 and CYP3A5(97). However, there is a lack of in vivo DDI studies carried out in people with CF so much of the data is derived from in-vitro studies, from healthy volunteers, or extrapolated from how other members of the same drug group act(10). Van der Meer et al compared the interaction between ivacaftor and selected CYP3A4 inhibitors in healthy controls and people with CF. They found that clarithromycin had a much smaller effect on ivacaftor exposure than ritonavir (used as the standard strong inhibitor in drug interaction studies)(96), suggesting that the dose adjustment suggested by the manufacturers, which is the same for both clarithromycin and ritonavir, might be too much, with potential for underdosing of ivacaftor(98). A case report used tezacaftor/ivacaftor TDM to rule out a clinically relevant interaction between tezacaftor/ivacaftor and clofazimine, and thus avoid an unnecessary dose reduction(99).

There is also an evolving adverse effect profile emerging in people with CF, specifically around psychological effects including anxiety, low mood, 'brain fog' and insomnia which may or may not be attributable to elexacaftor/tezacaftor/ivacaftor(100-103). Symptoms have been reported in those with and without a history of mental health problems. The mechanism for these effects is unknown, however given their lipophilicity they may cross the blood-brain barrier and have a direct action on CFTR in the brain, or on 5-HT2C receptors, as shown in animal models(102, 104). Spoletini et al used dose reductions of elexacaftor/tezacaftor/ivacaftor to manage these side effects in their patients(101). In the absence of TDM sweat chloride was closely monitored as an indirect measure of effect, to ensure that by reducing the dose to ameliorate adverse effects efficacy wasn't compromised. Other strategies employed in published literature to date include discontinuing, changing dose or

timing of administration and switching elexacaftor/tezacaftor/ivacaftor to either ivacaftor/tezacaftor or ivacaftor(100, 102). This might suggest that elevated levels of elexacaftor/tezacaftor/ivacaftor or indeed elexacaftor alone may be responsible for these effects, however since none of the reports to date measured elexacaftor/tezacaftor/ivacaftor concentrations it is not possible to establish causation. A recent literature review carried out by Choong et al, found that dose reduction, in the absence of TDM, had been used as mitigation for an adverse effect in 10% of publications reporting adverse effects of CFTR modulators(16). The authors postulated that the lack of TDM may be due to a 'lack of robust evidence on target levels, validated quantification methods, guidelines to monitor drug levels and poorly described indications for TDM'.

The ability to carry out TDM for CFTR modulators, is key as part of our armoury to manage these adverse effects. It can also provide fundamental knowledge about the PK/PD of these medicines in special populations, to enable individualised dosing and provide more cost-effective management, particularly given the huge cost burden of these medicines to health services. One such population is those with CF related liver disease whom were excluded from phase III clinical trials. Although real-world data has shown a significantly lower prevalence of hepatobiliary complications in those treated with ivacaftor(9) and improvements in markers of liver function in a cohort on ivacaftor/lumacaftor, some of which had CF liver disease(105), recommendations from the manufacturers of these medicines recommend that dose reductions be made based on Child-Pugh score, a marker of the severity of liver disease, though this is largely inapplicable for children with CF liver disease(106). This leaves clinicians unsure of what dose to use, and where the availability of TDM would contribute to the evolving knowledge of how we optimise doses by balancing efficacy and toxicity.

A new facet of CF care comes with the increasing pregnancy rates in women with CF since the introduction of ivacaftor(107). Although the use of CFTR modulators is 'off label' in pregnancy, there is emerging data supporting the continuation of modulator therapy to prevent clinical decline during pregnancy(107, 108). With the potential for altered pharmacokinetics during pregnancy, data from the ongoing MAYFLOWERS sub-study looking at the pharmacokinetics of

elexacaftor/tezacaftor/ivacaftor in pregnancy, at birth, and during lactation in both mother and infant will allow the determination of PK-PD parameters of this modulator in pregnancy and breastfeeding(109). However, with the high inter-individual variability seen in those that are not pregnant(93-96), TDM may still be necessary to personalise elexacaftor/tezacaftor/ivacaftor dosing during this critical time.

There are currently no commercially available assays, though several groups have published assay methods (99, 110-112). With the potential application for TDM of CFTR modulators widening, availability of an accessible routine assay is key to ensure that we optimise the use of these highly expensive and effective medicines.

3 Conclusion

For this unique population, where medicine use is so integral in preventing disease progression, a lack of research into the fundamentals of pharmacokinetics and pharmacodynamics of drugs used to manage CF in children from the outset has led to a disparity in treatment regimens used and relied on the use of TDM to best tailor treatment regimens. With the growing interest in pharmacokinetic modelling and more sophisticated TDM methods there is an opportunity to optimise many medicines, both new and old, used for children with CF.

4 Expert Opinion

Recommendations for drug dosing in children are based on a combination of efficacy data in phase II and III trials in adults, the availability of paediatric PK data and safety data. Despite extensive legislation incentivising pharmaceutical companies to invest in paediatric research for both new and existing drugs, the proportion of clinical trials in the European clinical trial database EudraCT that include children increased from 8.25% in 2007 to 12.4% in 2016 so still a long way to go(113). To date a lack of dosing recommendations in children has led to the use of 'scaled down' adult doses where PK/PD data is scarce. This is just as relevant for disease specific PK/ PD data with CF as a prime example of this. The result of this is widely differing practices globally as a result of a lack of consensus as to how to optimise a particular medicine for a child with CF, with risks of ineffective treatment regimens

and increased risk of adverse effects. In the wider healthcare context, inappropriate dosing can increase resistance. An analysis of the rate of azole resistant *A.fumigatus* isolates in a specialist respiratory centre, found the highest rate was in the 11-20-year-old age group(114).

TDM is often utilised in children with CF to optimise dosing when clearly defined dosing regimens, and the data to support these, doesn't exist. In the absence of this data TDM has been used in numerous publications to feed into population and physiologically based PK modelling to identify demographic and disease specific variables, and the subsequent use of models to simulate initial dosing regimens for children with CF. Although TDM may still be required to account for inter-individual variability it would be anticipated that the burden for repeated blood tests be diminished with benefits for both the child and the resources required if there is a higher likelihood that the starting dose may be sufficient - an important consideration for developing nations where resources might be scarce or technology lacking. Combining both of these methods BF combines a priori population-based data with a posteriori individual patient data to inform a patients dosing regimen, with accurate predictive outcomes(115). There is also increasing interest in the use of genomics testing to identify differences in PK and PD response to antibiotics and side effects which may be related to the genetic variability of individuals. In particular, polymorphisms in genes encoding for enzymic metabolism of drugs and membrane transporters(116). The association of this patient specific information with BF might be the key to truly personalised dosing. We should also not forget the need to gain an in-depth understanding of the relationship between exposure and response to establish clinically useful plasma concentration values for optimum clinical outcomes – an area where there is still limited research in children with CF. Even with the most sophisticated modelling systems if the TDM target value is incorrect it will negate the opportunity to optimise clinical outcomes.

There is also much potential to be gained from further research into alternative non-invasive methods of TDM, particularly in a population where 'needle phobia' is prevalent(117). Although there has been limited success with methods such as saliva for TDM of aminoglycosides(118), it has shown promise for the TDM of voriconazole(119, 120). Saliva was used as an alternative to serum voriconazole

concentrations in 10 adult patients, one of whom had CF(119). Linear mixed modelling revealed strong agreement between voriconazole concentrations in saliva and unbound plasma voriconazole concentrations and was subsequently borne out in a population pharmacokinetic model(120). Breath metabolomics are also being investigated as an extension of TDM for some anti-epileptic drugs (121), and if applicable to drugs used by children with CF, would be a welcome addition to the TDM armoury.

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