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Review

A year in review: Real world evidence, functional monitoring and emerging therapeutics in 2021

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1. Infection with SARS-CoV-2

In the year 2021 the SARS-CoV-2 pandemic has impacted us all, including people with cystic fibrosis (PwCF) and health care providers. International epidemiology studies have improved our understanding of the clinical sequalae of SARS-CoV-2 in CF. The European data registry reported on 130 PwCF (adults and children) with confirmed SARS-CoV-2 between February and June 2020 [1]. Overall, the incidence of infection was 2.70 per 1000 in PwCF which was greater compared to age-matched controls in the general population, although this figure may reflect more frequent testing in the Cystic Fibrosis (CF) population. Of those with SARS-CoV-2 infection, just over half (58%) of PwCF required hospital admission and 9% intensive care support, which was again greater than reported in the general population. This figure may reflect a more cautionary approach to hospitalize PwCF for observation. Those PwCF who had undergone lung transplantation or were immunocompromised were associated with an adverse prognosis. Of the five PwCF who had died, three were lung transplant recipients. A history of transplantation was associated with higher rates of hospitalization (82% *versus* 53%) and intensive care support (26% *versus* 5.6%) than those PwCF without transplants [1]. Other studies have shown that PwCF with lower lung function, lower body mass index (BMI), and with comorbidities such as diabetes or liver disease were also more likely to have severe infection [2,3]. The Cystic Fibrosis Registry Global Harmonization Group reported data on 105 children with SARS-CoV-2 infection from 13 countries over a 6-month period [3]. Over two thirds of children had a mild self-limiting illness which was managed in the community. Children who were hospitalized had a lower lung function and lower BMI, and no deaths were attributed to COVID-19 [3]. Thirty-seven percent of children were treated with oral antibiotics and 46% received intravenous (IV) antibiotics. Overall, studies showed the majority of PwCF with SARS-CoV-2 infection maintain their lung function and were managed with antibiotics either at home or in the community [1–3].

Overall, PwCF fared better than our initial expectations. PwCF were advised to shield in the first wave and areused to meticulous infection control measures, which may have been beneficial during the first wave. It has also been suggested that CFTR mutations may have protective mechanisms, such as increasing levels of angiotensin-converting-enzyme-2 messenger RNA in the airway epithelium reducing proinflammatory cytokines, which may mitigate infection severity [4,5]. Others hypothesized that SARS-CoV-2 may dysregulate the epithelial sodium (ENaC) and CF transmembrane conductance regulator (CFTR) channels leading to increased lung edema, which could have led to worse clinical outcomes. Thankfully, this does not seem to have come into fruition.

2. Impact of COVID-19 on clinical care

The SARS-2-CoV2 pandemic has led to significant changes in health care delivery for PwCF. A widespread surge in 'tele' or digital health has occurred [6,7]. In general, this has been reason-

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ably successfully implemented and accepted by PwCF and care providers, particularly adults [8–12]. Health care providers and PwCF have adapted to home spirometry, remote microbiological sample collection, blood monitoring and video consultants well [7,10,13]. Advantages include less risk of cross infection and convenience for PwCF who are clinically well [10,14,15]. However, disadvantages have also been highlighted. Home spirometry is estimated to be 2.0 (95% CI: 0.3 to 3.5%) percentage points lower than clinic spirometry [16]. Over half of adults and parents/carers for PwCF express concerns about lack of in-person assessments such as lung function and microbiological testing [10]. Other disadvantages include the lack of ability to perform a physical examination, difficulties in microbiological surveillance, and the loss of subtleties in communication that may get lost without face to face contact, particularly where there is a language barrier [7,9–12,14–16]. Pediatric teams and parents have been less likely to advocate for remote consultations and have raised concerns regarding monitoring adherence, safeguarding issues, and engaging teenagers [8,9,12,14]. Disparities in high speed internet access and technology may create a 'digital divide' [9,12,17]. Whilst the surge in telehealth has subsided and confidence in returning to face to face visits has grown, in person consultations will probably not return to pre pandemic levels [6,10–14]. Health care delivery has evolved and there is much work to do with evaluation and implementation of new hybrid models that address the individual needs of PwCF. This will have financial implications for health care providers [15,18]. It will be important to include patient reported outcome measures as well as home monitoring and adherence work in these new models [17,19].

3. CFTR modulators

We have gained further insight into the effects of CFTR modulators through *in vitro* studies, through clinical trials, and through use of real-world data. Studies have shown the *in vitro* effect of elexacaftor (ELE) consists of corrector and additional potentiator activity, in human bronchial and nasal epithelia of PwCF with Phe508del mutation, class III gating mutations, and rare mutations [20–22]. These preclinical studies suggest clinical benefit in patients with the above-mentioned mutations [20–22]. Conversely, *in vitro* results of some rare missense mutations show no additional effect on the adding of ELE, suggesting there will be no clinical benefit to the addition of ELE to tezacaftor-ivacaftor (TEZ-IVA) [23]. These studies support the use of *in vitro* models as a precision model, to predict the most beneficial combination of modulators for rare mutations and support the role of *in vitro* testing for clinical approval of modulators. This is further supported by a study that assessed the use of nasal epithelial organoids [24]. A strong correlation between functional correction and clinical response was observed. However, the type of epithelial cells used for the culture of organoids seems important: two studies showed no correlation between intestinal organoid swelling and clinical response in different CFTR mutations [25,26].

More data has been published on elexacaftor-tezacaftor-ivacaftor (ETI) therapy in younger PwCF and those with residual function mutations. In children with CF aged 6–11 years, a 24 week phase 3 trial assessing the safety, pharmacokinetics and efficacy of ETI in 66 PwCF homozygous for *Phe508del* or *Phe508del* with a minimal function mutation showed that safety and pharmacokinetic profile were comparable to older patients [27]. The efficacy is shown by the improvement of perecent predicted forced expiratory volume in 1 s ($ppFEV_1$) with a mean of 10.2% in a group with mean FEV1 at baseline of 88.8%. Furthermore, lung clearance index (LCI) decreased by 1.7 units and there was a significant improvement of sweat chloride and CFQ-R respiratory domain response. These results strongly support the use of ETI in this young patient group. A recent publication has described the effect of ETI as compared with ivacaftor (IVA) and TEZ-IVA (active controls) in patients $>$ 12 years with Phe508del gating and residual function genotypes in a 8 week trial [28]. Mean $ppFEV_1$ and sweat chloride improved by 3.5% and 23.1 mmol/l respectively in 132 patients receiving ETI compared with 126 active controls.

Open-label extension and real world studies in PwCF with lumacaftor (LUM)-IVA aged 2–5 years and 6–11 years homozygous for *Phe508del*-CFTR mutation and TEZ-IVA aged $>$ 12 years homozygous or heterozygous for *Phe508del* mutation confirmed the overall safety of the modulators [29–32]. The efficacy on clinical outcome parameters were sustained over up to 120 weeks and results of a real-world study was comparable to open label studies. The PROMISE study, a post-approval study investigating real world experience of ETI, described six months into treatment of 487 PwCF $>$ 12 years and $\geq$ 1 *Phe508del* mutation [33]. Significant improvements in $ppFEV_1$ (mean change 9.8%), sweat chloride (mean change 41.7 mmol/l), BMI and, CFQ-R respiratory domain were observed. The largest improvements were seen in PwCF naïve for modulators and on dual-modulator therapy (LUM-IVA or TEZ-IVA), compared to PwCF on IVA. The results of ongoing data collection up to 30 months after the start of ETI and sub studies investigating the effect of ETI across a wide range of CF disease manifestations will be reported in future.

Further studies have been published in PwCF and advanced lung disease (ALD) on ETI therapy [34,35]. Of note is the French prospective observational study of PwCF $\geq$ 12 years with ALD ($ppFEV_1$ $<$ 40) who started ETI [35]. Data were collected before, 1 and 3 months after starting ETI. ETI was initiated in 245 PwCF with a median $ppFEV_1$ of 29%. Rapid clinical improvement was seen with a mean increase of $ppFEV_1$ of 15%. There was a significant decrease in need for long-term oxygen, non-invasive ventilation, and enteral tube feeding. Importantly, a twofold decrease of lung transplantations was observed compared to the two years previously, with a stable number of deaths without transplantation. Although these data need to be confirmed over a longer period, they suggest that ETI can have a major impact on life expectancy, even in patients with ALD.

With the widespread roll out of CFTR modulators, real world data has provided insight into extrapulmonary manifestations of these therapies. These include increases in weight, improvements in sinus symptoms, lower insulin requirements in CF related diabetes and higher conception rates [36–40]. We are improving our understanding of the impact of CFTR modulators on gastrointestinal symptoms, gut physiology and the lung and gut axis but there is still much to learn [41–47]. Furthermore, there are reports of unintended extrapulmonary consequences of CFTR therapies. These include transfer across the placenta and into breast milk [48]. There are limited data on the safety of these therapies in pregnancy or when breast feeding. Whilst early data on 45 pregnancies reports no serious adverse events, we eagerly await the results from the MAYFLOWER study to aid informed treatment decisions in pregnancy [49].

4. Extrapulmonary complications

As the disease trajectory in CF improves and PwCF are living longer, attention shifts towards emerging co-morbidities and aging with CF. As PwCF age, they are at increased risk of cancers, particularly of the gastrointestinal (GI) tract [50]. Organ transplantation and CF related diabetes are independent risk factors for lower GI malignancy, suggesting that earlier screening may be beneficial in this population [50]. Furthermore, cardiovascular complications, obstructive sleep apnea, osteopenia and skeletal fragility are all emerging problems [51–55]. Addressing mental health issues and promoting emotional wellness warrant ongoing attention,

particularly as those with depression are at increased risk of death [56–61].

5. Diagnosis

At the other end of the age spectrum, updated guidance on the management of children with CFTR-related metabolic syndrome (CRMS)/ CF screen positive inconclusive diagnosis (CFSPID) has been published [62]. The major change is the advice to have detailed assessment at age 6 years of those newborns with initial sweat chloride concentration above 50 mmol/L and one CFTR mutation; these should be monitored with repeated sweat tests and combined with genetic and functional investigations [63].

6. Early lung disease

The availability of CFTR modulators has further increased the interest in detecting and monitoring early lung disease, and several modalities are currently being evaluated. These include multiple breath washout (MBW), computer tomography (CT) and magnetic resonance imaging (MRI). MBW has proven to be more sensitive than spirometry to detect early CF lung disease and can be used to track disease progression and treatment response in young PwCF [27,64–66]. The most widely used technique is the nitrogen washout (MBNW), which was used to assess the efficacy of modulators in phase 3 trials in children [27,67,68]. Concerns have been raised about the accuracy of commercially available MBNW devices because their primary outcome parameters, functional residual capacity (FRC) and LCI, show significant differences between each other and compared to body plethysmography [69,70]. One of these devices (Eco Medics AG, Duernten, Switzerland) had significant sensor errors leading to a mean overestimation of FRC and LCI of 8.9% and 11.9%, respectively [71]. A software update, including a correction algorithm, for this device was released. The impact of this correction on existing clinical trial data has been described [72]. Across intervention studies treatment effects remained statistically significant, although the magnitude of the difference was smaller. Observed treatment effects and interpretation did not change after the correction, which is reassuring for past and future trials.

MBW, CT and MRI have all been used to monitor the treatment effect of CFTR modulators [73–75]. MRI and MBW again have been shown to be more sensitive than FEV_1, especially when the treatment effect is of modest size [74,76]. In a study of MBNW in ALD during treatment with ETI, MBW outcome parameters showed larger improvements than $ppFEV_1$, suggesting the main treatment effect takes place in the peripheral airways [77]. Longitudinal studies confirm that MBNW, CT, and hyperpolarized (129) xenon MRI are all able to detect disease progression in preschool children and children and adolescents with CF [78–80]. A study implementing deep learning scoring of CT scan reported promising results to improve reproducibility and could lead to a significant decrease in the time consuming manual scoring of CT scans in future [81].

7. Pulmonary exacerbations

The diagnosis and management of pulmonary exacerbations (PExs) remain a major topic of interest. STOP2 reported that shorter duration of antibiotic therapy for PExs is not inferior to longer courses [82]. Almost 1000 adult PwCF were enrolled and randomized based on their clinical response after 7–10 days of intravenous antibiotic treatment. The study assessed $ppFEV_1$ change from baseline to 2 weeks after antibiotic cessation. For those who had an early robust response to treatment, 10 days was not inferior to 14 days of antibiotic treatment. For those who did not have an early robust response, 21 days was not superior to 14 days of treatment. In addition, no differences were observed across the antibiotic durations and time to next PEx. This suggests that treatment durations may be reduced safely in PwCF, which may reduce treatment side effects, decrease treatment burden, and reduce treatment costs. PwCF who did not have an early robust response often showed no drop in $ppFEV_1$ at the time of diagnosis suggesting FEV_1 may not be the best marker to diagnose PExs and to monitor treatment response for all. LCI appears to be a more sensitive marker of PExs for preschool children and for those with early lung disease [83,84].

In addition to functional testing, work on biomarkers and symptom scores continues into the diagnosis of PExs and monitoring treatment response. Conflicting data on the effectiveness of CRP as a biomarker have been published. In the STOP2 study, CRP was not a good predictor for a PEx diagnosis, whereas others have proposed a step wise algorithm using CRP thresholds and fold-change from stable may be used to diagnose a PEx when there are conflicting data between changes in lung function and symptoms [82,85]. Whilst this review does not permit us to examine all potential biomarkers in detail, the Biomarker Special Interest Working Group published a review highlighting neutrophil elastase, IL-8, TNF-α and IL-1β as valid biomarkers of lung inflammation. Other potential biomarkers such as Il-6, calprotectin, SPLUNC1 and calprotectin in serum, and HMGB-1 and YKL-40 in sputum require further evaluation [86–89]. The STOP-OB study showed that the Chronic Respiratory Infection Symptom Score (CRISS) in PwCF treated for PExs improved and exceeded the minimal important difference in almost 94% of the included patients, suggesting this could be a very useful tool in the evaluation of PExs [90]. Thus, selection and validation of combination scores is of great importance to be clinically useful in routine practice.

8. Microbiology

New data show that genetic variants located in other CFTR genes are associated to earlier first acquisition of *P. aeruginosa* [91]. Some single nucleotide polymorphisms in DCTN4, TNF and SLC9A3 appear as risk factors for *P. aeruginosa* infection [91]. This may be a step towards predictive and preventive medicine with better identification of PwCF at high risk of early infection and chronic colonization.

Work has continued on understanding the complex polymicrobial communities in the CF lung, the impact of treatments on the microbiome and its relationship with disease severity [92,93]. Preliminary studies show that CFTR modulators are associated with modest changes in the CF microbiome [94,95]. ETI treatment is associated with increased population diversity and a reduction in the ratio of pathogens to anaerobes [94]. IVA treatment is associated with a higher density of strict anaerobic bacteria and an increase in richness and diversity [95]. However, more data are needed to understand the longer-term impact of CFTR therapies on community structure.

In future, the integration of functional or “omics” technology may improve our understanding of host and microbiome interactions [96]. The functional response of the community dictates response to therapy, affects clinical outcomes and provides potential novel therapeutic targets and potential novel biomarkers [96]. For example, specific virulence factors produced by *P. aeruginosa*, the alkyl quinolones, are promising biomarkers for pulmonary *P. aeruginosa* and are also potential therapeutic targets [97–99]. As more studies confirm that *P. aeruginosa* persists in airways of ‘eradicated’ patients, we anticipate that focus may switch from attempting to eradicate infection, towards manipulating the functional response of the microbiome [100].

9. Novel therapies

Bacteriophage therapy has evolved such that it could be a promising tool against antibiotic-resistant bacteria [101,102]. Due to potential phage-resistance in the bacterial host, strategies including phage cocktails, which combine multiple phage isolates targeting different phage receptors, and combining phages with selected antibiotics are being explored [103–105].

Advances are underway for those without a commercially available CFTR modulator therapy. The HIT-CF initiative is evaluating CFTR modulators in populations with rarer genotypes [106]. Other therapeutic strategies being explored include RNA therapy, gene editing and gene therapy for those with rarer mutations, including nonsense and missense mutations [107]. Most of these approaches are in pre-clinical development or early clinical phases. There are many challenges to be overcome before these can be safely used in clinical practice [107].

Work is needed to identify the most accurate *in vitro* and *in vivo* tests to predict CFTR function and clinical response to help guide individual personalized therapies. This may include a combination of organoid technology, sweat chloride concentration, nasal potential difference and intestinal current measurement [24,76,108–111]. It is anticipated that by investigating genetic and non-genetic modifiers, we may improve our understanding of phenotypical variation in response to CFTR therapy [112,113].

These advances may also help with evaluation of those on the milder end of the spectrum, like the children with CFSPID [62]. This leads to the question of where do we draw the line with CFTR dysfunction and the clinical need for CFTR modulator therapy? Should we be prescribing CFTR modulators to treat extrapulmonary manifestations, such as in post lung transplant recipients, when the evidence base is so small? It is important that we use evidence-based medicine to justify expensive treatment regimes, particularly when finite resources are available in nationalized health care systems.

Finally, a combination of the SARS-2-CoV pandemic and the worldwide roll out of CFTR modulators has shown the CF communities ability to adapt to a fast-paced change in the CF landscape. It has highlighted our ability to use international collaborations and registry data to understand the impact of these changes in the real world. We are working closer with the CF community to develop novel patient reported outcomes for clinical trials [114,115]. We need to continue to listen to what is important to PwCF and engage them in shared decision making, including balancing their treatment burden. Given the pace of change, it is vitally important we work together to consider innovative approaches to clinical trial designs to ensure we can continue to optimize CF care in future [116–118].

Declaration of Competing Interest

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