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A year in review (2022): Modulators and COVID19, the story goes on…

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Introduction

In this review we have aimed to cover some of the highlights of the cystic fibrosis (CF) literature in 2022, which again has been dominated by the SARS-CoV-2 (COVID-19) pandemic and modulator therapy. We have also explored other themes, such as novel findings in relation to pulmonary exacerbations, early lung disease and emerging areas for people with CF (pwCF).

COVID-19

Literature in 2022 confirmed that overall pwCF fared better than expected with COVID-19; although some did suffer severe consequences of COVID-19, it did not appear that infection worsened CF respiratory disease.

A systematic review of the risk factors for severe COVID-19 disease in pwCF [1] identified the main risk factors for hospitalization included percent predicted forced expiratory volume in 1 second ($ppFEV_1$) <70, CF-related diabetes (CF-RD), age >40 years, pancreatic insufficiency, lower body mass index (BMI) and previous lung transplant. In the pediatric CF population lung function and BMI Z-score were both found to be significantly lower in hospitalized children, compared to non-hospitalized ones. The use of dornase alfa was associated with decreased risk of severe disease, while there was insufficient evidence to establish the role of inhaled steroids or Cystic Fibrosis Transmembrane Conductance Regulator protein (CFTR) modulators. An international observational study [2], including 1,452 pwCF in 22 countries (421 children; 32 pregnant women), had similar findings, with worse outcomes independently associated with $ppFEV_1$ <40, older age, non-white race, low weight, previous transplant and CF-RD. Those on highly effective CFTR modulators were less likely to be hospitalised with oxygen, likely reflecting the overall clinical improvement as a result of these drugs. The impact of COVID-19 on respiratory outcomes in pwCF was described in a multicentre prospective study with 26 pwCF with RT-PCR confirmed infection compared to 42 with a RT-PCR negative test [3]. At six months follow-up there was no significant difference in changes in mean $ppFEV_1$ or in the probability of pulmonary exacerbations (PEx) between groups.

Although COVID-19 did not severely impact the respiratory health of the CF population, it clearly affected the clinical care model. An analysis of the CF Foundation Patient Registry described changes in care during the COVID-19 pandemic [4]. During the one-year period following March 15, 2019 there was a significant drop in the number of in-person visits (from a high of 91% to a low of 9%). 25% of pwCF were not seen in person at all during 2020. Of interest, they noted that lung function and BMI were higher in 2020 than in 2019 for children aged 6 to <12 years and pwCF eligible for Elexacaftor/Tezacaftor/Ivacaftor (ETI), again reflecting the impact of the CFTR modulators.

Finally, an Australian longitudinal cohort study [5] compared trends in outcomes before and after the onset of the pandemic, using national registry data from 3662 pwCF (children and adults). $ppFEV_1$ changed from a mean annual decline of -0.13% to a mean improvement of 1.76%. The annual trend in BMI also improved and the number of hospitalisations decreased from a total of 2656 to 1957.

CFTR modulators

Unsurprisingly, the benefits of CFTR modulator therapy were featured in the literature throughout the year, highlighted by publication of standards of care for CFTR variant-specific therapy [6]. New information widened the scope of usage for mod-

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ulator therapies and the standards highlight the various eligibility criteria for each of them. In addition, they stress the importance of evaluating pwCF with variants of unclear significance, in view of the absence of treatment for those with non-response variants.

The added benefits of the triple modulator ETI compared to a dual modulator combination (Tezacaftor/Ivacaftor (TEZ/IVA)) were demonstrated in patients 12 years of age and older and homozygous with F508del with improvements in a quality of life measure, specifically the respiratory domain of the revised Cystic Fibrosis Quality of life score (CFQ-R) [7]. The difference was substantial (17.1 vs. 1.2) when the minimal clinically important difference is reported to be 4 points.

Longer term data from real world studies is also starting to emerge, verifying the results demonstrated in initial studies. Nichols et al. enrolled 487 patients aged 12 or over, with at least one copy of the F508 allele, in a prospective, observational study over 30 months [8]. This demonstrated improvements of a similar magnitude to randomized controlled trials with an increase in $ppFEV_1$ of 9.8% (CI 8.8 – 10.8) and an increase in CFQ-R score of 20.4 (CI 18.3 – 22.5).

Measures of nasal potential difference and intestinal current in adult patients (half of whom had two F508 alleles and half of whom had one F508del allele and one minimal function allele) taken before and after starting ETI found that CFTR function was restored to between 40–50% of normal across both measurements and both cohorts [9]. In a separate study, the effects of treatment on lung clearance index (LCI) and magnetic resonance imaging (MRI) scores found a statistically significant, and clinically relevant, improvement in LCI in patients with either one or two F508del alleles, extending to those who had previously been on TEZ/IVA. In the group as a whole, LCI improved from 10.3 (IQR 8.0 to 13.2) to 7.4 (IQR 6.5 to 10.3), representing a relative improvement of 23.4%. MRI global scores also showed statistically significant improvements across both groups, mainly reflecting improvements in mucous plugging with only a trend towards improvement in perfusion scores [10].

Initial ETI studies excluded patients with severe disease, but following on from their previous study in 2021, a French group published their 12-month data on ETI use in people with advanced lung disease [11]. Of 65 transplant candidates, 61 remained free from transplantation due to rapid clinical improvement, $ppFEV_1$ increased 13.4% (peaked at one month and remained stable), mean BMI increased by 2.6 kg/m^2, and there was a 91% decrease in hospitalization days. At the end of the study, only 30% and 20% still required supplemental oxygen and non-invasive ventilation, respectively. Therefore, the improvement in survival is demonstrated, with a marked decrease in transplants and deaths without transplantation in pwCF.

There is also mounting evidence for the use of ETI post-transplant. A study of 90 lung transplant recipients revealed that the most frequent indications were sinus disease and gastrointestinal (GI) symptoms [12]. Almost half of the patients (42%) stopped ETI (median 56 days) most commonly, due to GI symptoms, respiratory symptoms, or lack of perceived benefit. Only 3% stopped ETI due to elevated liver enzymes. Drug interactions were also an important consideration, with tacrolimus being the most commonly implicated drug, needing to be decreased in 47% of cases. In the case of liver transplantation, case series have shown an improvement in respiratory symptoms and quality of life, although close monitoring is necessary for adverse events, the most common being elevation of liver function test (LFTs) and increased concentration of the immunosuppressant, so gradual dose titration is warranted [13].

Initial trials looking at ETI focused almost exclusively on respiratory outcomes. However, there is interest in their effect on other organs with an increasing number of publications on the topic, although not always with concordant results. A single centre, observational study looked at gastro-oesophageal reflux and sinonasal symptoms in a cohort of patients with advanced CF [14]. All 32 pwCF showed improvements above the minimally important clinical difference in all three patient reported outcome measures. However, the much-anticipated PROMISE study told a different story regarding GI outcomes. It included data on 438 participants from 56 centers and showed no meaningful clinical difference in patient reported outcomes after six months of treatment, despite reaching statistical significance [15]. As such, the effect on GI symptoms remains unclear. This is particularly relevant for pwCF post-transplant, where modulator therapy may be considered for GI symptoms alone.

Real world data have reported side effects associated with ETI that were not evident from the initial pivotal studies. A case series of 266 pwCF treated with ETI [16] identified 19 subjects who presented with a deterioration in mental health, including symptoms such as anxiety, low mood, insomnia and “brain fog” with reduced attention and concentration span. Four subjects ultimately stopped ETI and 13 underwent a dose reduction of ETI; only two continued on full dose. Rapid resolution or improvement in mental health occurred in 10/13 cases (77%) who had dose adjustment. Of note, 12 of the 19 pwCF (63.1%) had a past medical history of anxiety and/or low mood, suggesting there are patients who are greater risk for development or worsening of anxiety and/or depression, but the authors also hypothesized there may be an association with individual variation in elexacaftor metabolism and increased systemic CFTR expression.

The impact of ETI on fertility in women with CF is well-known and there is emerging data on the safety of ETI on the fetus as women often remain on the drug throughout pregnancy. Given the knowledge that ETI passes through the placenta and into breast milk and the observation that ETI was associated with cataract development in fetal animal models, it is a potential adverse event of interest. One study carried out in two centers (USA and Israel) undertook routine screening for cataracts in 23 newborns of mothers treated with ETI [17]. In three cases the newborns exposed to ETI in utero and with breast feeding were found to have congenital bilateral cataracts, although none had significant visual impairment. Cataract development was not observed in infants treated with IVA aged $\geq$4 months. The authors propose a cataract screen for newborns exposed to ETI in utero and through breast feeding, along with counseling of pregnant women on ETI.

This passage through the placenta has also been used as a method of treatment. A pregnant F508del carrier with a F508del homozygous fetus received ETI at 32 weeks gestation, after a meconium ileus was evident on ultrasound at 23-weeks [18]. Bowel dilation resolved by imaging on treatment day 27, and a female infant was delivered vaginally at 36 weeks with no complications.

Finally, many hope that treatment with ETI will allow us to reduce treatment burden for patients. The SIMPLIFY study aimed to assess the effects of discontinuing nebulised hypertonic saline or dornase alfa, measured by the 6-week change in $ppFEV_1$ in those with baseline $ppFEV_1$ $\geq$60%. The study authors acknowledge that six weeks is a short time period, but hoped this approach would maximize adherence to the treatment regimen. 847 participants were randomized to continue or discontinue treatment, and they found no clinically meaningful differences in pulmonary function between the two groups. The results were strengthened by the absence of clinically important changes in LCI, Chronic Respiratory Infection Symptom Score (CRISS) and CFQ-R Respiratory Domain Score. Respiratory adverse events were more prominent in the small subgroup with lower lung function ($ppFEV_1$ 60–70%) [19].

Focusing on children, the efficacy and safety of ETI has been demonstrated in a Phase 3b multicentre study that included 121 pwCF between 6 and 11 years of age, heterozygous for F508del and a minimal function CFTR mutation. In the 61 children treated with ETI for 24 weeks, efficacy was proven by a decrease in the primary endpoint $LCI_{2,5}$ -2.29 units compared to placebo group -0.02 units. Consistent with the findings in older pwCF there was improvement of sweat chloride test (SCT) (-52.1 mmol/l vs -0.9 mmol/l) and $ppFEV_1$ (+9.5% vs -1.5) and CFQ-R domain score. The most common adverse events were headaches and cough, and one child stopped treatment because of a rash. There were therefore no new safety findings and ETI was well tolerated in this age group [20].

In the same age group (6-11 years) a multicentre open-label extension study for 96 weeks looked at the long-term safety, tolerability and efficacy of treatment with TEZ/IVA in 109 children homozygous for F508del or heterozygous for F508del and a residual function CFTR variant. 99.2% of the children had ≥1 treatment-emergent adverse event that was, in general, mild to moderate. Only five children (3.8%) had an adverse event that led to treatment discontinuation. The improvements in LCI, SCT, and in $ppFEV_1$, seen in the parent studies remained stable supporting the long-term use of TEZ/IVA in children aged ≥6 years with the above genotypes [21].

Finally, an open-label Phase 3 study explored the safety, pharmacokinetics (PK), pharmacodynamics, and tolerability of Lumacaftor/ivacaftor (LUM/IVA) in children aged 1 to <2 years with F508del homozygous genotype. PK analysis in 14 children confirmed the appropriateness of dosing regimen. Overall, 44 of 45 children had an adverse event, which were mild (52.2%) or moderate (39.1%). The most common adverse events were cough (34.8%), infective PEx (21.7%), pyrexia (21.7%), and vomiting (17.4%). Five children (10.9%) had serious adverse events of which one was considered possibly related to LUM/IVA (distal intestinal obstruction syndrome). As secondary endpoints the decrease of SCT concentration from baseline to 24 weeks treatment was -29.1 mmol/l and improvements in biochemical measures of exocrine pancreatic function could be seen [22].

PwCF ≥6 years with certain genotypes not eligible for ETI were the focus of the VOCAL observational study, which analyzed the long-term effect of Ivacaftor (IVA) in pwCF with selected non-G551D-CFTR gating mutations in a real-world setting. In 65 pwCF treatment with IVA was associated with improvements in $ppFEV_1$ (+10.8%), BMI (+0.79 kg/m^2), and BMI-for-age z-score (0.54) in the first six months of treatment. It also led to decreases in PEx rates in the first year, and reductions in the prevalence of respiratory infections in the first 1 to 2 years. Safety results were consistent with common clinical manifestations of CF and the known safety profile of IVA [23].

Pulmonary exacerbations

Despite the improvements seen with highly effective modulator therapy, PEx remain an important area of interest. There continues to be an evidence gap to guide best practice in treating exacerbations and several studies have been published this year attempting to provide more evidence.

Further analysis of the data from the STOP2 trial [24] sheds light on two important issues – the difference between delivery of treatment in hospital versus at home and treatment of PEx secondary to Pseudomonas aeruginosa (PsA); both analyses were performed retrospectively. The former examined where treatment had taken place, categorizing patients into one of three different groups – treated in hospital only, treated in hospital and at home, and treated at home only. The data appear to favor treatment in hospital with those treated only at home having a significantly lower increase in $ppFEV_1$ following treatment, and patients treated in hospital more likely to be classified as "early robust responders" (based on changes in $ppFEV_1$ and symptom score). Whilst there are important limitations to this study, it raises questions about how we should optimize the delivery of home therapy.

The second study looked at a subgroup of patients culturing PsA (751 pwCF) [25]. CF treatment guidelines recommend the use of two antimicrobials when treating PEx, but objective evidence to support this recommendation is lacking. In this analysis, antibiotic therapy was categorized into classes (e.g. beta-lactams, aminoglycosides, quinolones). Patients were then grouped by the number of different classes, and the combination of different classes they received. Data were also collected looking at whether additional agents were added to the initial treatment regimen. Only 50 patients (6.7%) were started on a single class of antibiotic, with 552 (73.5%) started on two classes and 149 (19.8%) started on three or more. Somewhat unsurprisingly the addition of an additional agent mid treatment was associated with a lower $ppFEV_1$ response. In terms of outcome, the authors used the odds of retreatment within 30 days as a surrogate for treatment failure, finding that this did not differ as a function of the number of classes administered. These data also suffer from limitations, but supports previous smaller studies in suggesting that it is time we re-evaluate the risk/ benefit of treatment using multiple antibiotic classes.

Keeping with this theme, a single-center, retrospective, cohort study analyzed the effect of changing antibiotics during treatment for PEx. They examined 399 events, 105 of which included a change of antibiotics [26]. The primary outcome was the absolute and relative change in $ppFEV_1$ at the end of treatment and follow-up, with the proportion of patients returning to >90% or >100% of their previous baseline as a secondary outcome. In the non-responders, a change in antibiotics was not associated with a significant difference in primary or secondary outcomes. The results of the study imply there is a subgroup of patients that are slow/poor responders regardless of antibiotic choice, and that further research into the determinants of poor response to treatment would be beneficial.

"Prevention is better than cure", and the CF Health Hub study team published a paper studying the effect of a self-management intervention aimed at supporting adherence, and its effect on PEx. This was a multicentre, controlled study of 607 pwCF, randomized either to usual care (with monitoring of adherence) or to the intervention arm (tailored, multi-component self-management, along with monitoring of adherence). The intervention arm led to improvements in adherence with an adjusted mean difference in adherence of 9.5% (8.6% - 10.4%); however, the overall adherence rates in both arms remained disappointingly poor, a sober reminder of the challenges of sustaining a rigorous and often complicated treatment regimen. It is therefore no surprise that there was a non-significant difference in the primary outcome (rate of PEx) [27].

Early lung disease

In an effort to understand the role of respiratory viruses in the pathogenesis of early CF lung disease a study was performed to evaluate the association between the presence of viruses in the lung and airway abnormalities on computerized tomographic (CT) over the first year of life [28]. No correlation was identified between detection of viruses (RSV, rhinovirus, parainfluenza, coronavirus or human metapneumovirus) and any of the PRAGMA-CF subscores (a CF-specific quantitative CT scoring system). However, there was an association between respiratory symptoms and early airway wall thickening (wheeze and cough) and atelectasis (cough and lower respiratory tract symptoms).

A multicentre, randomized, double-blind, placebo-controlled study hypothesized that continuous treatment with azithromycin three times per week would reduce structural lung damage at age 36 months, as estimated by CT [29]. The two primary outcomes were the prevalence of bronchiectasis and the percentage of airways disease severity, with similar results in both groups. However, azithromycin did reduce the use of intravenous, inhaled and oral antibiotic cycles each year and hospitalizations, and there was a reduction in inflammatory markers. They did not observe any emerging bacterial resistance to antibiotics.

Finally, hypertonic saline in preschool children aged 3-6 years also showed improvements that could be measured on CT with a significant difference in PRAGMA-CF subscores (disease severity, degree of bronchiectasis and air trapping) [30].

Emerging areas

Data from the US CF Foundation patient registry (2000 - 2019) was used to explore trends in obesity in the CF population. A relative decrease in underweight status by ~40% could be seen, as well as a >300% increase in overweight status, and >400% increase in obesity. Out of a total of 13,742 pwCF aged 20 years and older, those who were obese had a higher proportion of milder CFTR mutations (class IV-V), were more likely to be pancreatic sufficient and diagnosed later in life, and suffered fewer PEx. All these factors suggest a milder severity of their overall condition without evidence of causality. Due to the period studied there were only a few pwCF treated with CFTR modulators [31].

It is likely, however, that these results will be exacerbated by the introduction of ETI therapy. The effect of ETI on weight and BMI was examined in a single center, retrospective study in 134 pwCF. The mean BMI increased from 23.6 to 25.2 with an annualized difference in BMI trajectory of 1.47 kg/m^2/year. This translates to a shift in the number of people with a normal weight towards being overweight and obese. They also measured blood pressure, HbA1c, and lipid profiles with mixed results including improvements in some parameters (HbA1c for pwCF without a history of CF-RD, and HDL) but an increase in the number of patients with hypertension and increases in total-cholesterol and LDL. With an aging CF population this suggests that we are likely to see an increase in cardiovascular and cerebrovascular disease, which has previously been rare in pwCF [32].

Finally, despite the excitement surrounding the advent of highly effective modulator therapy, there are still 15-20% of individuals world-wide that are not able to benefit from this form of treatment. This has been highlighted as a research priority at both the European Cystic Fibrosis Conference and the North American CF Conference, and it is evident that the CF community is committed to finding treatments that are agnostic of genotype. Several different novel approaches are being pursued [33] and it is not yet clear which of these will progress to viable treatment options. However, the hope is that over the next few years we will start to see results that will lead to highly effective treatment for all pwCF.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr Dorothy Grogono reports a relationship with Insmed Inc that includes: consulting or advisory. All three authors participated in the ADVANCE 2022 educational programme (sponsored by Vertex).

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