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REPORT FROM

European Cystic Fibrosis Conference 2022

Thursday June 30, 2022

CF physician's perspective

After 2 years of online conferences, the 45th ECFS Conference was finally back as a physical meeting in Rotterdam in the Netherlands, providing cutting edge science and breakthroughs in CF from around the world. With 30 symposia, 2 plenary sessions, 24 workshops for selected abstracts and 6 meet the expert sessions, this year's scientific program was buzzing with activity.

The main theme of the conference was how the future will look post highly effective CFTR modulator treatment and post COVID pandemic. There was agreement that the CF world is a different place than the last time the conference was held in Liverpool in 2019. The most positive outcome of COVID were the improvements in E-health seen across Europe that have connected patients and physicians in new ways creating opportunities for different ways of delivering health care. The main question on everyone's mind was however the reporting of the first real-world experiences with elexacaftor/tezacaftor/ivacaftor (ETI) for CFTR variants. As it turns out, it is still early days, but Professor Pierre-Régis Burgel from France lifted the vail on some of the first real world data from the French CF cohort showing apparent large shifts in morbidity and mortality, with many CF patients with end-stage lung disease being able to leave transplantation lists due to improvements in lung function and health. However, it seems that many questions regarding long-term safety and effectiveness, particularly in patients with advanced lung disease, liver disease, renal insufficiency, or problematic bacterial infections remain unanswered. While patients are clearly expectorating less mucus after ETI, less is understood about what happens to those chronically infected. The impact of CFTR modulators on other important outcomes such as concurrent treatments, chest imaging, or pregnancies are also eagerly awaited and several centers ae getting ready to report. Improvements in the understanding of the genetic complexity of the CFTR gene and how the proteins fold were reported including continuing improvements in diagnosis across Europe. New born screening and improving registry data means that over 52.000 persons in Europe are now included in the CF Patient Registry.

New treatment modalities were presented including on antibiotic combination therapies in the management of people with CF and new ways of sensitizing apparently resistant bacteria, for example through hyperbaric oxygen therapy. Advances in using whole genome sequencing to predict phenotypic P. aeruginosa infections and a novel *Mycobacterium abscessus* treatment were presented giving hope to patients suffering from multidrug resistant bacteria. Novel imaging modalities for use in clinical trials, ethical aspects of genetic screening and nutrition and liver disease in CF were other highlights at this year's conference.

A main organizational challenge put forward by the conference organizers was how to ensure recruitment and retainment of young doctors

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and scientists to the field. Two young scientists who were recognized this year were Peder Berg from Denmark and Alessandra Murabito Italy who received the prestigious Gerd Döring Award for exceptional early career European scientists.

The ECFS Award 2022 was given to Professor Kris De Boeck from the University of Leuven in Belgium for her outstanding contribution to the understanding of cystic fibrosis and her work with the CF Clinical Trials Network. The number of reviewed protocols in the CTN is increasing, included 12 commercial protocols from 6 different companies and 3 protocols from investigator-initiated projects (HIT-CF-Europe, CAR-CF and CF-Storm). A final highlight was the speech by Jacquelien Noordhoek from the CF patient organization who told the story of how the European patient organizations had positively impacted CF care and helped scientific efforts through the years. She went on to point to the need for ECFS support to similar efforts in Turkey and the Middle East, where new born screening is being rolled out. Never have the CF patient organizations been more important as many hundreds of patients with CF and their families have fled the war in Ukraine requiring comprehensive organizational support across Europe.

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Report from the European Cystic Fibrosis Conference in Rotterdam, 8-10 June 2022

PART 1

This report presents the 45th European CF Conference as seen through the eyes of a patient organisation representative who has not been medically trained but acquired some knowledge through real-life experiences with a family member with CF and some autonomous learning on the subject. The range of the symposia was extensive and sophisticated. As a disclaimer I would like to express that my interpretation of the speeches in various symposia may be incorrect. Any misinterpretation is solely based on my lacking expertise in the highly specialised scientific and medical detail. Should any such flaws emerge, I hope to be corrected promptly. You can contact me at: leena.virtanen(at)hengitysyhdistys.fi.

The opening plenary introduced the audience to where CF science stands at the moment. Conference president, Professor Harm Tiddens, stated the urgency of permanent movement. He ran the audience through the advances of CF medicine through his years in the profession starting with the discovery of the CFTR gene in 1989 through the latest advances in CFTR modulator therapies. Professor Kris De Boeck awarded recent research in CF and inspired the audience with highlighting the steps forward in CF research. She even suggested some book tips that help put in perspective where we are in tackling universal global challenges.

Out of the abundance of talks I will start with Symposium 1 entitled CF *Research in the roaring twenties.* The second speaker, Dr. George Retsch-Bogart from Chapel Hill, US, asked the question "Repair vs. modulation: What is best?"

To start with, he stated that there are four strategies to treat CF: targeting 1) the DNA, 2) the RNA, 3) the CFTR protein, and lastly 4) the CF manifestations or symptoms. Traditional CF therapy has only been able to target the symptoms before the advent of highly effective modulator therapies in the previous decade. The speaker's question concentrated on the first three targets.

Among the challenges with targeting the DNA and RNA in genetic trials are the following: In relation to **preclinical data** there is the need to ask what information is required to move into early phase clinical trials. What is the role of health benefit exchanges? What about the role of animal models as human response to human antivirals cannot be tested on animals?

When these strategies are developed, there are further issues with **study designs:** 10 % of the CF community can participate. What is the role of healthy volunteers? What about the patients who are on modulator therapy? How will the prolonged follow-up be managed? There are **education and ethical** questions. The study teams and CF Community need to be educated. How will the ethics of participation in early phase studies be assessed? There are also variable risks concerning

mRNA/LNP (lipid nanoparticle vector for mRNA delivery), AAV (adeno-associated virus vectors for gene delivery), lentivirus and editing, for example.

However, these are the notable **research priorities** for the genetic era:

- epithelial biology, cell types and targeting technologies
- thresholds required for efficacy
- vector technologies to accomplish efficient delivery
- advances in genetic cargo
- animal models to facilitate and predict clinical translation
- outcome measures for genetic-based therapies
- clinical trial designs in highly effective modulator era
- defining risks of transient and permanent genetic-based therapies

Studies to target the CFTR protein in new modulator programmes are ongoing at the preclinical phase and phases 2, 3 by three companies. There is also research in readthrough and antisense oligonucleotide agents (ASO) that are commonly classified under restoring CFTR function. But where do they actually fit?

The clinical evidence for patients on highly effective modulator therapies (HEMT) (ivacaftor and elecxacaftor/tezacaftor/ivacaftor = ETI) is very strong. There is a probable change in the natural history of cystic fibrosis for these patients.

The comparison between **repair** of DNA/RNA and **modulation** of the protein brings out multiple issues related to CFTR variant, age, tolerability, availability. As for CFTR variant, modulation is very dependent on it, whereas repair might even be independent of the variant. At present, modulation may be applied to babies aged as young as four months and older, whereas repair in future may probably be possible for adolescents aged 12 or 18 years and older. Modulation is already available, unlike repair. The treatment target of modulation is systemic while repair is initially thought to be targeted at the lung. Is repairing the lung enough?

Regarding side effects, drug-drug interactions and long-term effects, repair can only offer unknowns. There is data on the side effects of modulation, such as hepatic transaminases, rashes and mental health consequences. Depending on the modulator combination there are some drug-drug interactions. There is also some information and concern about possible long-term effects of modulators. Modulation requires daily dosing, whereas repair can be successful with daily, weekly, or monthly doses, or might even be a one-off fix in the future.

Is the original question between these two approaches unfair? You might not be eligible for a modulator or tolerate it, you might be too young or not responding. For some people today the answer may be both, for optimal results. Tomorrow it might be different.

Fortunately, progress continues in both therapeutic approaches, and the community remains strongly committed to solving this.

Leena Virtanen
Patient Organisation Representative, Finland

Report from the European Cystic Fibrosis Conference in Rotterdam, 8-10 June 2022

PART 2

I would like to express as a disclaimer that any misinterpretation of the speeches in various symposia is completely mine and solely based on the absence of education and expertise in the specialised scientific and medical detail. Should any such flaws emerge, I hope to be corrected promptly. You can contact me at: leena.virtanen(at) hengitysyhdistys.fi

The advent of CFTR modulator therapies or variant specific therapies (VST) had marked a paradigm shift in CF care for many people with CF. They are the talk of the town. However, these therapies are not helpful to about 10 % of the patients worldwide and this proportion of Finnish people with CF is even higher. Approximately as many as 30 % of the Finnish CF population are not eligible for modulator therapies (K. Malmivaara, V. Elenius; *Lääkärilehti [Finnish Medical Journal]* 2021; 40; 2220-2224).

Being able to target the basic root cause of the disease has made all the difference for numerous patients. I selected topics connected with the impact of CFTR modulator therapies. The take-home message was that they have resulted in prolonged and significant improvements in key clinical outcomes.

Symposium 7 dealt with *Infection beyond CFTR modulators*. After the talks of three speakers (G. Héry Arnaud, S. Gräber and E. Zemanick) the conclusion was that especially two modulator therapies, ivacaftor and triple therapy (elexa/teza/iva; ETI) correlated with varying degrees of decrease in some of the bacterial pathogens, such as *Stafylococcus aureus (S.a.)* and *Pseudomonas aeruginosa (P.a.)*, and even one mention of NTM (E. Zemanick). It still remains to be seen whether the reduced bacterial burden is sustained. In these studies no eradication took place.

Traditional outcome measures may not be sufficient any longer in monitoring lung infection management or detecting changes in mild disease with patients on modulators: Spirometry might not be sensitive enough, pulmonary exacerbations may be too infrequent, sputum cultures are difficult to obtain. Potential new options could be lung clearance index, imaging (MRI, CT), alternatives to sputum such as exhaled air condensate samples or serology. Remote monitoring such as home spirometry, cough monitors and wearables could provide more frequent testing.

You can find a more detailed discussion of Symposium 7 **here**.

Symposium 20 discussed Real World Data with CFTR modulators. Dr. L. Nährlich (Germany) discussed the learnings from post-authorisation studies (PAS) concerning ivacaftor, luma/iva, teza/iva and only for a short while the triple therapy (ETI). The registries include all patients, regardless of compliance, which is not included as an outcome measure in registries. He concluded his talk with the lessons learnt. With a highly effective modulator treatment (HEMT) there is less

progression of the severe lung disease. Pulmonary infections decrease but are not eliminated. Comorbidities decrease but need to be screened. Reduced mortality is still up for confirmation. Safety in pregnancy has to be shown.

Plain language glossary for cystic fibrosis and clinical trials has been a project between the CF Europe, CF Trust (UK) and ECFS Clinical Trials Network born out of an idea in 2019. It came up from a discussion about a European Medicines Agency (EMA) rule that anyone 12 years and older should be able to understand a summary of any clinical trial or study. A team was set up, terms and their definitions were tested in groups of teens and adults with no or some knowledge of CF. The team also gathered feedback from representatives of pharmaceutical companies in the CF Round Table of Companies. Basing on the results and work a glossary was devised. See the original glossary here: cfeurope.eu/what-we-do/glossary

By clicking *Read more* the user will find more detailed explanations. With some entries they can follow one more click *(Read our article)* and find very illustrative images and educational graphics, for instance on the whole process of CFTR (cystic fibrosis transmembrane conductance regulator) formation, the flaws caused by gene variants and the therapies for specific mutations.

The launch was presented in a Tomorrow Lounge Session on Friday 10/6 by PhD, Head of Research at CF Europe Elise Lammertyn, science writers Fiona Dunlevy, PhD, and Jade Ashton, who also disclosed her personal motivation and journey to this task. Showing us listeners the picture of her mother as her inspiration, she shared the starting point where her mother had an infant with CF in her arms, and no knowledge of medical science, but ended up having a degree within seven years.

In the closing plenary of the conference Professor Kevin Southern introduced the ECFS standards for the provision of CFTR modulators prepared by a multi-disciplinary and international editorial group and revised by stakeholders. The introduction of this therapy has resulted in prolonged and significant improvements in key clinical outcomes. We are living in an interim period for standards of care with disparities in access to, eligibility for and efficacy and adverse effects of the variant specific therapy (VST).

The introduction to VST must always be closely monitored by the healthcare team. The patient and/or their carers need to be counselled on anticipated impacts on airway clearance, idio-syncratic and often transient physiological but also psychological effects as well as nutrition.
For patients with non-responsive variants *ex vivo* testing may inform potential for response in some patients, but the standard, symptomatic care should not be compromised. The care team should keep aware of and involved in clinical trials of novel VST or genetic therapies. Negotiations in states or countries on reimbursement may include a cost-effectiveness assessment. The processes may lead to discrepancies in access. The ECFS recommends that the processes around access should be in the public domain and result in globally equitable access for all eligible people with CF.

The second speaker in the closing plenary of the conference was Dr. Jeffrey Beekman, “Mr HIT-CF”, leader of the organoid studies in Utrecht. He discussed what is next in CF research and treatment.

He presented some interesting figures. There are approximately 162,000 people with CF in the world on an estimate. This is based on the existing registries and where these do not exist on estimated live birth incidences in parts of the world like Asia, Africa, Latin America. 65 % of an alleged number of people with CF are diagnosed, and 12 % of them are receiving the triple combination modulator treatment (Guo et al, Journal of Cystic Fibrosis). Consequently, a significant number of people with CF live in areas where the best therapy is unavailable.

More than 2000 CFTR variants are known, and less than 500 have been typed and assessed as causing cystic fibrosis. More than 1000 variants cause disease in less than 5 % of all patients.

Dr. Beekman dealt with the separate **stages** of the CF pathophysiology and the therapeutic opportunities for them, and whether there is CFTR mutation specificity. Apart from the **gene defect** stage, one challenge involved at each of the other stages is efficacy.

1. **The CFTR gene defect** might be treated with gene therapy targeted at all mutations where the delivery would be challenging, applying gene therapy with locus-specific repair. It could be performed on most mutations and be organ-specific. Gene editing approaches are already being adapted *in vivo* outside CF. There is a novel medicinal VX-880 islet cell therapy developed for cancer correction, and the question is whether this could also be applied to correcting the defects in pancreatic cells in CF. **The CFTR mRNA defect** could be treated with readthrough agents (with nonsense mutations).

2. The CFTR protein defect is being treated with correctors and potentiators as well as dual acting compounds for a few classes of mutations (trafficking and gating). Challenges with efficacy emerge especially with rare mutations. Challenges are, in addition to efficacy, lacking access for rare variants or non-responsive individuals, side effects and irreversible phenotypes. HIT-CF project offers a European solution opportunity for rare mutations based on individual tissue, and this study is still ongoing.

3. Defective ion transport might be treated with alternative channel modulators for any mutations, and cAMP potentiators for selected residual function mutations, but defining the identity of the target is challenging.

4. Mucus plugging is being treated in all mutations with mucolytics. The challenge is that these are local applications.

5. Infection and inflammation are addressed in patients regardless of mutation with traditional/symptomatic therapies: antimicrobials and anti-inflammatory agents with varying degrees of efficacy, and lastly with lung transplantation where one issue always is organ compatibility.

Dr. Beekman greeted the input of young research talent with delight and their achievement as this will shape the future.

Leena Virtanen
Patient Organisation Representative, Finland

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