RESPIROLOGY

CARE™ PERSPECTIVES

ERS/NACF 2018

A FOCUS ON CYSTIC FIBROSIS

Abstract Summaries and CARE™ Perspectives provided by the CARE™ Respirology Faculty

ERS 2018 - EUROPEAN RESPIRATORY SOCIETY INTERNATIONAL CONGRESS - **PARIS, FR** - SEPTEMBER 15-19
NACF 2018 - NORTH AMERICAN CYSTIC FIBROSIS CONFERENCE - **DENVER, CO** - OCTOBER 18-20

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ERS/NACF 2018

INTRODUCTION

This CARE™ Perspectives Conference Report has been developed by Dr. Hartmut Grasemann, a member of the CARE™ Respirology Faculty, who recently attended the European Respiratory Society (ERS) International Congress 2018 and the North American Cystic Fibrosis (NACF) Conference 2018 held in Paris, France and Denver, Colorado, respectively. With a focus on Cystic Fibrosis, this report provides a summary of compelling stories and abstracts presented at ERS and NACF 2018, framed from a Canadian perspective.

The abstracts have been summarized and then augmented with Faculty perspectives.

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CARE™ (Community Academic Research Education) believes in accessibility, competition, innovation with new treatments and the optimization of current therapy- with the goal of improving patient outcomes. CARE™ initiatives aim to educate Canadian health care professionals by providing updates on relevant medical news and developments, framed from a Canadian perspective.

This report is written in the language in which the content was presented. The content and graphics included within each section of the report are drawn from the presentations made by the respective presenters at the 2018 ERS and NACF Conferences.

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REPORTS ON CLINICAL AND PATIENT REPORTED OUTCOMES OF IVACAFTOR, LUMACAFTOR/IVACAFTOR AND TEZACAFTOR/IVACAFTOR THERAPY IN CF PATIENT POPULATIONS

ERS 2018. OA312: Lung clearance index (LCI) in children = 12 years old with cystic fibrosis (CF) taking ORKAMBI® at University Hospital Limerick (UHL)

M. Mulligan et al.

CARE™ Summary of Abstract: The aim of this study was to investigate the efficacy of two lung function tests, the multiple breath washout (MBW) and routine spirometry in assessment of ORKAMBI® therapy in the paediatric CF population. A significant improvement in average LCI (by -1.72, $p < 0.05$) was noted, but no difference in FEV_1 pre- and post-ORKAMBI® treatment. The authors concluded that MBW is more sensitive than spirometry in assessment of the pulmonary effect of ORKAMBI® in the paediatric CF population. ORKAMBI® (lumacaftor/ivacaftor) has been commercially available for CF patients over 12 years of age in Ireland since May 2016.

CARE™ PERSPECTIVE: Cystic fibrosis lung disease starts early in life and effective interventions are therefore an important goal in pediatric CF care. Using routine pulmonary function testing to demonstrate efficacy of therapies in patients with mild lung disease can be challenging. For example, FEV_1 can stay normal despite significant structural lung damage. More sensitive methods are therefore needed for the assessment of early or mild lung disease in clinical practice and as new endpoints in clinical studies.

ERS 2018. OA312. LCI and $ppFEV_1$ values for pre- and post-ORKAMBI®

	pre-ORKAMBI®	post-ORKAMBI®
LCI median (range)	11.25 (7.41 – 14.33)	8.32 (7.73 – 13.45)
$ppFEV_1$ median (range)	82.5% (49.5% – 103.0%)	86.8% (48.5% – 106.5%)
LCI mean ± SD	11.14 ± 2.30	9.41 ± 2.35
$ppFEV_1$ mean ± SD	79.6% ± 17.4%	81.1% ± 21.6%

NACF 2018. 26: Real world effectiveness of ivacaftor in pediatric cystic fibrosis patients

L. Greenawald et al.

CARE™ Summary of Abstract: Retrospective chart review of 26 patients aged 2-18 years (mean age 9.5 yrs), in 4 Nemours CF centers, treated for FDA-approved CFTR mutations with ivacaftor therapy. Reviewed outcomes included sweat chloride levels, lung function and nutritional parameters at an average of 10 months, intravenous (IV) antibiotic use and respiratory tract microbiology over 1 year on therapy. Fifteen patients had Class III CFTR mutations (58%), 5 patients Class IV mutations (19%) and 6 patients Class V mutations (23%). Ivacaftor resulted in a decrease in sweat chloride levels and improvement in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) by 11% in 4 months. IV antibiotic use declined by 85% over 1 year ($p = 0.03$). The proportion of patients growing gram-negative bacteria decreased from 46% to 19% whereas methicillin-resistant staphylococcus areus (MRSA) persisted in 80% of patients. Variations in response were noted between classes of mutations, specifically patients with Class V mutations (n=6) showed marginal improvement in FEV_1 and decline in BMI.

CARE™ PERSPECTIVE: Monotherapy with the CFTR potentiator ivacaftor which is approved for a growing number of gating mutations, sets the bar for future CFTR targeting therapies designed for common mutations. Currently approved double combination therapies have less significant effects on mean pulmonary function but variable responses in FEV_1 have also been noted.

ERS 2018. PA1322: Real life experience of lumacaftor/ivacaftor in adult Phe508del homozygous cystic fibrosis patients

G. D. M. Bonizzoni et al.

CARE™ Summary of Abstract: Single center experience with lumacaftor/ivacaftor therapy in eight adult CF patients homozygous for Phe508del. Lumacaftor/ivacaftor reduced hospitalization rates (1.57 ± 0.48 vs 0.86 ± 0.34, $p = 0.027$) and number of days on IV antibiotics (22.87 ± 6.23 vs 12.88 ± 4.642, $p = 0.028$). Sweat chloride, BMI and respiratory symptom scores improved. Lung function as assessed by spirometry did not change.

CARE™ PERSPECTIVE: This study highlights that improved outcomes with CFTR-targeting therapies in real life experience may not be associated with an improvement in lung function, when assessed by spirometry.

ERS 2018. PA3414: Retrospective analysis of treatment with Ivacaftor/Lumacaftor in patients with cystic fibrosis at the Munich Cystic Fibrosis Centers

S. Naehrig et al.

CARE™ Summary of Abstract: Retrospective analysis of change in ppFEV$_1$, glycated hemoglobin (HbA1c), c-reactive protein (CRP), leucocyte counts, and pressure of oxygen (pO$_2$) in 56 patients treated with lumacaftor/ivacaftor, including 11 children younger than 18 years of age. Response to therapy was variable. Changes in ppFEV$_1$ ranged from - 8.11% to +10.75%; the mean change in ppFEV$_1$ was 0.77%. No significant difference in CRP, leucocyte counts or HbA1c was seen. Eighteen patients (32%) had to discontinue the treatment, mainly because of bronchial obstruction but also because of interactions with other drugs (itraconazole for treatment of allergic bronchopulmonary aspergillosis, ABPA). ORKAMBI® was approved for CF patients over 12 years of age in Germany in November 2015.

CARE™ PERSPECTIVE: This study further supports the concept that while some patients experience significant improvements in lung function, the average impact of lumacaftor/ivacaftor therapy on pulmonary function measured by spirometry is moderate. The high rate of unwanted side effects leading to discontinuation of therapy of therapy is a concern.

ERS 2018. PA3415: Effects of lumacaftor-ivacaftor therapy on CFTR function in Phe508del homozygous patients with cystic fibrosis

S. Gräber et al.

CARE™ Summary of Abstract: This prospective observational study assessed clinical outcomes including FEV$_1$ % predicted and BMI, as well as CFTR biomarkers including sweat chloride concentration, nasal potential difference (NPD) and intestinal current measurement (ICM) before and 8-16 weeks after initiation of lumacaftor/ivacaftor therapy. After initiation of therapy, sweat chloride concentrations were reduced by 18 mmol/L, and NPD and ICM showed partial rescue of CFTR function in nasal and rectal epithelia to levels of 10% and 18% of normal, respectively. All patients improved in at least one CFTR biomarker, but no correlations were found between CFTR biomarker responses and clinical outcomes. No improvement was seen in FEV$_1$ % or BMI.

NACF 2018. 251: Effects of lumacaftor/ivacaftor in cystic fibrosis patients homozygous for f508del CFTR mutation

P. Melotti et al.

CARE™ Summary of Abstract: Single center observational study from Verona, Italy, involving 47 CF patients aged 13-48 years, treated with lumacaftor/ivacaftor. This group observed a mean increase in absolute FEV$_1$ of 2.6% (± 8.4 SD), a BMI increase of 0.3 (± 1 SD), a weight increase of 1.1 kg (± 2.6 SD) and a reduction of pulmonary exacerbations requiring IV antibiotics or hospitalization of 0.8 (± 0.9 SD), compared to the year before treatment initiation. In four patients the treatment was suspended because of adverse effects, most frequently thoracic oppression. The authors concluded that the effects on relevant clinical outcomes were achieved at levels that are consistent with the results obtained in previously published clinical trials.

NACF 2018. 308: Effects of tezacaftor/ivacaftor treatment in patients with cystic fibrosis and f508del/f508del-CFTR: Patient-reported outcomes in a phase 3 randomized, controlled trial

Y. Yang et al.

CARE™ Summary of Abstract: This study examined the impact of tezacaftor/ivacaftor on disease-related symptoms, functioning, and well-being as measured by Cystic Fibrosis Questionnaire–Revised (CFQ-R) in patients with CF homozygous for F508del-CFTR (F508del/F508del). Data from 504 patients were included who participated in EVOLVE (NCT02347657), a phase 3, randomized, double-blind, placebo-controlled trial, evaluating tezacaftor/ivacaftor (100 mg QD/150 mg BID) in F508del/F508del CF patients aged ≥12 years. CFQ-R consisting of 12 domains, including respiratory symptoms, was assessed at baseline and weeks 4, 8, 12, 16, and 24 after initiation of treatment. Tezacaftor/ivacaftor therapy resulted in benefit across a broad range of patient-reported health outcomes beyond respiratory symptoms, including physical functioning.

CARE™ PERSPECTIVE: These findings may support the value of CFTR targeting therapies in CF patients but there is still a need for effective therapies that result in significant improvements in lung function and survival.

"TEZACAFTOR/IVACAFTOR THERAPY RESULTED IN BENEFIT ACROSS A BROAD RANGE OF PATIENT-REPORTED HEALTH OUTCOMES BEYOND RESPIRATORY SYMPTOMS, INCLUDING PHYSICAL FUNCTIONING."

CLINICAL AND PRECLINICAL STUDIES ON CFTR TARGETING THERAPIES

NACF 2018. 213: Phase 2 safety and efficacy of the triple combination CFTR modulator regimen VX-445/ TEZ/IVA in CF

J. L. Taylor-Cousar et al.

NACF 2018. 216: Phase 2 safety and efficacy of the triple combination CFTR modulator regimen VX-659/ TEZ/IVA in CF

J.C. Davies et al.

CARE™ Summary of Abstract: These two studies evaluated the efficacy and safety of two Vertex triple combination therapies in adult patients with CF and either *F508del/F508del* or *F508del*/minimal function CFTR genotypes. The two multicenter clinical studies were developed in parallel and shared similar study design and primary safety and efficacy endpoints.

In the study by Davies et al, patients with *F508del*/minimal function, for which there is currently no approved CFTR modulator therapy, were randomized to 80, 240 or 400 mg of VX-659 in triple combination with tezacaftor/vacaftor vs. triple placebo for 4-weeks. Patients with *F508del/F508del* were treated with a 4-week tezacaftor/ivacaftor run-in phase, prior to being randomized to 4-weeks of additional therapy with VX-659 (400 mg) or placebo.

The Taylor-Cousar et al study followed the same interventions by genotype scheme with the exception that VX-445 was used for the *Phe508del*/minimal function genotype in doses of 50, 100 or 200 mg, and 200 mg was used for the *F508del/F508del* genotype. Compared to placebo, 4-weeks of triple combination with VX-659 increased FEV_1% predicted by an average of 13.3 and 9.7% in the *Phe508del/* minimal function and homozygous genotypes, respectively. Similarly, triple combination with VX-445 significantly increased FEV_1% by 13.8 and 11%. Both drug combinations were well tolerated.

CARE™ PERSPECTIVE: In summary, these studies demonstrate that triple combination therapies of two correctors with ivacaftor for patients carrying the most common CFTR mutation can safely achieve greater FEV_1 improvements than currently approved double combinations. Both studies were recently also published in the NEJM (D. Keating et al, NEJM, 2018, 379:1612-1620; J. C. Davies, NEJM, 2018, 379:1599-1611). If these results can be confirmed in phase 3 trials, which are currently ongoing, they represent a major break-through in the treatment of most individuals with CF. Approval of triple combination therapy in the US is expected for 2019.

"IF THESE RESULTS CAN BE CONFIRMED IN PHASE 3 TRIALS, WHICH ARE CURRENTLY ONGOING, THEY REPRESENT A MAJOR BREAK-THROUGH IN THE TREATMENT OF MOST INDIVIDUALS WITH CF."

NACF 2018. 289: Evaluation of Galapagos-AbbVie CFTR modulators using intestinal organoid assays

M. C. Hagemeijer et al.

CARE™ PERSPECTIVE: Galapagos (GLPG) and AbbVie (ABBV) are developing a triple combination therapy of a CFTR potentiator and two complementary acting correctors. Two distinct sets of correctors with complementary mechanisms and different potentiators are in development. Testing of these combination therapies in primary human bronchial epithelial cells resulted in promising improvements of CFTR function in vitro. A clinical trial to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of a triple combination treatment (GLPG 2451, GLPG2222 + GLPG2451) in subjects with CF is in underway.

NACF 2018. 196: Splice switching antisense oligonucleotides for the treatment of cystic fibrosis

W. Michaels et al.

CARE™ Summary of Abstract: Splice switching antisense oligonucleotide (SSO) technology has emerged as a novel therapeutic strategy in personalized medicine to modify gene expression by modulating pre-mRNA splicing. One splicing-related mutation in CFTR is the 3849 + 10kb C > T splice mutation. In this experiment an SSO was designed to target the cryptic splice site created by 3849 + 10kb C>T mutation in differentiated primary patient-derived bronchial epithelial cells. When analyzed in comparison to current FDA approved CF drugs ivacaftor and ivacaftor/lumacaftor, SSO treatment resulted in a greater increase in CFTR function compared to that achieved with either CFTR modulator treatment.

CARE™ PERSPECTIVE: Approximately twelve percent of CFTR mutations are mutations that alter pre-mRNA splicing. The U.S. Food and Drug Administration (FDA) approved the use of ivacaftor for people with CF who have and at least one of five splice mutations in 2017. The study by Michaels et al demonstrates that SSO technology has the potential to result in better CFTR rescue than currently approved therapies.

NACF 2018. 15: Cystic fibrosis mutations located where the pore narrows disrupt CFTR conductance and gating, but are rescued by ivacaftor and lumacaftor

M. K. Al-Salmani et al.

CARE™ Summary of Abstract: This in-vitro study demonstrates that two CF mutations I336K and L927P, both located in the pore constriction, form protein kinase A (PKA)-activated CFTR Cl- channels gated by intracellular ATP. However, their single-channel behavior was characterized by defective conduction and gating. As a result, for both mutants open probability was reduced 6–8-fold compared to that of wild-type CFTR. Ivacaftor potentiated both I336K and L927P Cl- channels in excised membrane patches and enhanced I336K- CFTR-mediated transepithelial Cl- currents in CF bronchial epithelia. The corrector lumacaftor alone, and in combination with ivacaftor, substantially increased I336K-CFTR-mediated transepithelial Cl- currents in CF bronchial epithelial cell lines (CFBE), suggesting that correction of this structural defect markedly improves CFTR function. Thus, CF mutations located at the pore constriction severely disrupt CFTR function but are rescued by small molecule CFTR modulators.

CARE™ PERSPECTIVE: This is an elegant study demonstrating how in-vitro studies can be used to characterize rare CFTR mutations and predict response to CFTR targeting therapies. With an increasing number of available therapies, in-vitro assays may be helpful to predict responses to different drugs, which in an era of personalized medicine would allow for selection of the most promising therapy for an individual patient.

THE CORRECTOR LUMACAFTOR ALONE, AND IN COMBINATION WITH IVACAFTOR, SUBSTANTIALLY INCREASED I336K-CFTR-MEDIATED TRANSEPITHELIAL CL- CURRENTS IN CF BRONCHIAL EPITHELIAL CELL LINES (CFBE), SUGGESTING THAT CORRECTION OF THIS STRUCTURAL DEFECT MARKEDLY IMPROVES CFTR FUNCTION.

NACF 2018. 273: Results from two completed phase I studies with POL6014, a novel inhaled neutrophil elastase inhibitor

J. Karafilidis et al.

CARE™ Summary of Abstract: POL6014 is a novel neutrophil elastase inhibitor, administered as a nebulized drug via the Pari eFlow® system, in development for cystic fibrosis by Santhera Pharmaceuticals. In two Phase I studies, orally inhaled POL6014 was safe and well tolerated in both healthy volunteers and CF patients. The drug was safely administered to healthy volunteers in single doses ranging between 20 and 480 mg, and to clinically stable CF patients in doses ranging from 80 to 320 mg.

CARE™ PERSPECTIVE: While CFTR targeting drugs prove to be beneficial in cystic fibrosis, there is an ongoing need for effective treatments of symptoms and complications of the disease that are not resolved by the currently available drugs; these include anti-infective and anti-inflammatory treatments. Neutrophil elastase is an enzyme released by neutrophils and macrophages into the CF airways that causes lung damage and is associated with CF-bronchiectasis and poor outcome. Neutrophil elastase therefore is a logical target for new therapies that hold the promise of an anti-inflammatory effect altering disease progression.

ABOUT THE CARE™ RESPIROLOGY FACULTY

The CARE™ (Community. Academic. Research. Education) Faculty is a pan-Canadian group of leaders in their field who gather, discuss and address gaps in knowledge, to develop education initiatives that frame news from a Canadian perspective.

The vision of the CARE™ Faculty is to share opinions and update Canadian specialists with news and developments from key conferences framed in a Canadian perspective.

The mission of the CARE™ Faculty is to enhance medical education, with the explicit goal of improving patient outcomes.

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