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Journey to the Center of a Disease: The Cystic Fibrosis Saga

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Abstract

Since the first clinical description of the disease cystic fibrosis (CF) in 1938, there have been innumerable milestones in relation to delineation of disease pathogenesis and subsequent treatment which continue to this day. This narrative review: 1) details key discoveries that have significantly impacted overall CF patient health, 2) correlates these important advancements specifically to clinical observations from providers at the Penn State Health Milton S. Hershey Medical Center (PSH-HMC) adult CF program and 3) provides potential future directions since the regulatory approval of cystic fibrosis transmembrane conductance regulator (CFTR) protein therapies. With the availability of highly effective CFTR modulator therapies, providers from the PSH-HMC adult CF center have observed the following major changes in the health and lives of adult CF patients including: 1) improved survival, 2) reduced hospitalizations and 3) an increase in the number of women with CF successfully completing pregnancy, child-birth and subsequently entering into motherhood. This changing clinical landscape of all patients with CF will probably necessitate revisions in current practice patterns and adjustments by multiple care providers and care systems including the addition of providers previously minimally involved in CF patient care.

Keywords: Cystic fibrosis • Cystic fibrosis transmembrane • Conductance regulator • Protein modifiers

Introduction

The ongoing and truly epic saga of the disease cystic fibrosis (CF) and the millions of patients afflicted with this disease is punctuated by innumerable highlights and milestones that have continued to this day. Every institution, every medical center, every hospital, every practitioner in every setting has their truly unique stories and experiences to communicate. In this review we will 1) highlight landmark milestones in relation to understanding the disease CF and the subsequent impact upon patient care management, 2) attempt to link these remarkable accomplishments from the incredible journey of CF to the Penn State Health Milton S. Hershey Medical Center (PSH-HMC) adult CF program and 3) conclude by providing some thoughts for future consideration.

Background

Best original screenplay

In 1938, Dr. Dorothy Andersen identified a cohort of infants and children with predominately abdominal symptomatology and malnutrition and who died at an early age [1]. This observation led to the unique identification of a new disease, that being CF. These first identified syndrome of patients never survived long enough to manifest the other significant organ dysfunctions which we now know create the spectrum of health abnormalities for patients with CF. Subsequent clinical observations identified the disease CF as a multi-organ disease affecting all exocrine organs of the body with the basic pathological abnormality related to abnormal mucus and secretions.

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Best director

As the population of CF patients expanded, a "group of concerned parents" (www.cff.org) without any medical background nor societal affiliation astonishingly identified the need for a patient advocacy support organization for CF patients and formed the Cystic Fibrosis Foundation (CFF) in 1955. These humble roots have grown into the current penultimate CFF which remains the most widely acknowledged, most widely modeled and most respected disease specific patient advocacy organization in the entire world.

Best collaboration

For over 40 years since original disease description, there developed an expansion of the recognition of the clinical spectrum of disease manifestations for patients with CF but an absence of any significant scientific discoveries into disease pathogenesis and then subsequent therapeutic management. This changed dramatically in the early 1980s when Richard Boucher, MD, John Gatzy, PhD and colleagues working collaboratively at the University of North Carolina in Chapel Hill published a series of observations and experimental data in multiple prestigious journals identifying the physiological and biochemical abnormality with CF airway epithelial cells [2-4]. Astonishingly they accurately identified abnormalities in ion transport of electrolytes across the apical/abluminal service of polarized airway epithelial cells as the basic biochemical abnormality in CF, specifically a) deficient or reduced outward/external chloride transport and b) accelerated or exaggerated hyperabsorption/inward transport of sodium across these airway cells apical membranes. Based solely upon this physiological data these two investigators hypothesized (and subsequently validated many years later) that there must exist a complex membrane-bound protein on the apical service of airway epithelial cells ("the defect is transcellular") that controlled bi-directional ion transport which was abnormal in patients with CF.4 That putative hypothetical protein was subsequently termed "the cystic fibrosis transmembrane conductance regulator" abbreviated as CFTR. This terminology has persisted to this day as attribution to this landmark scientific discovery which little known at that time and which would eventually, 30 years later, total change the lives and survival of 90% of patients with CF.

Special achievement award

In 1989, in the journal Science (8 September 1989 245 Issue 4922) Dr. Francis Collins, Dr. Lap-Chee Tsui and colleagues published three articles identifying the discovery of the CF gene on chromosome 7 which encodes a

1480 amino-acid protein, termed CFTR. In the original publication only eight disease-causing mutational variants were reported but importantly included a 3-base pair deletion in the CF gene (i.e. the delta F508 mutation) that resulted in the absence of a single phenylalanine amino-acid at position 508 in CFTR: Phe508 del. Phe508 del mutation encompasses approximately 85% of all USA CF patient mutational variants either homozygous or compound heterozygous [5-7]. As a tribute to that sentinel discover, a 4-year-old boy with CF named Danny Bessette was pictured on the cover of that edition of Science 1989. The discovery of the CF gene then allowed for verification of the hypothetical CFTR protein and also allowed for expanded genetic analysis of all CF patients that to date has now revealed greater than 2000 CF gene mutations with approximately 100 such variants causing disease in over 95% of patients.

Best supporting roles

Through direct funding from the CFF, a number of therapeutic drugs began clinical development and eventual regulatory approval world-wide. This list includes dornase alfa (1993), inhaled hypertonic 7% saline, inhaled tobramycin in various formulations (1997), inhaled aztreonam in a specific formulation (2010); which drugs very quickly became incorporate into the standard of care list of lung health maintenance medications for all CF patients [8]. However, these therapies although with symptomatic benefit and ability to reduce hospitalizations had minimal effect upon disease modification since they all acted after the disease process already became fully manifest and not preventively.

Best lead performance

The lack of CF lung disease modification therapies came to an end when ivacaftor (termed a potentiator) became the first world-wide regulatory agency approved CFTR modular (2012) for a limited number of patients with certain specific gene variants (less than 5% entire CF population); however, even in this small group of CF patients the therapeutic potential of CFTR modifiers became all too obvious and evident. Additional combinations of CFTR modulators which included both potentiators such as ivacaftor and correctors such as lumacaftor, tezacaftor and elexacaftor soon emerged again with obvious and strikingly positive clinical benefit when added to prior available lung health maintenance medications. In contrast to previously approved inhalation medications as lung maintenance in CF lung disease which could only target the lung, these groups of potentiators and correctors were available as oral preparations with clinical benefits also evident in non-lung organs. Then in 2019 a triple combination CFTR modifier medication was granted regulatory approved (elexacaftor, tezacaftor, ivacaftor: ETI) which therapeutic agent has extraordinarily changed the clinical course for all drug-eligible CF patients. Importantly, the approval for this triple combination therapy (ETI) was expanded to include any patient with even a single deltaF508 mutation (homozygous and/or compound heterozygous) and ages as young 6 years. Thus, over a relatively short period of time CFTR modifiers were now available to almost 90% of all CF patients; however, note that these therapies do not reverse existent and often irreversible disease. Thus, for the first time pharmacological agents were now available to treat the early stage root causes of this disease at the molecular and biochemical level by altering and improving the function of CFTR protein but without gene modification (which still has not been achieved). Correctors function by increasing the quantity of functionally mature CFTR protein that is transported and affixed to the apical membrane of epithelial cells of all affected CF organs. Potentiators function by increasing the quality, efficiency or functionality of existent mature membrane-bound CFTR protein. Thus, the rationale for combination potentiator and corrector therapies should be evident. Proof of principle for these CFTR modifiers biological efficacy was validated by demonstration of marked reductions in sweat chloride measurements, frequently to values less than the pathological value of 60mmol/liter [9,10]. The maximum capacity of CFTR potentiators and correctors in each individual CF patient is limited by the quantity/amount of actual protein upon which they can exert their biological activities. In attempts to further increase the functional activity of CFTR protein and thus add improvement to current CFTR combination drugs in relation to clinical effectiveness and to overcome this protein substrate limitation, additional class of CFTR modifiers are currently in development but not yet regulatory approved called amplifiers. CFTR amplifiers function by upregulating the expression of CFTR-encoding mRNA so as to amplify production of increased volumes of actual CFTR protein.

Observations

The Penn State Health Milton S. Hershey Medical Center (PSH-HMC) Adult CF program began in 2001 with three total patients and approximately 5 years later received independent CFF-accreditation. To date this program has provided care to over 250 individual CF patients, at times with yearly patient census near 150 patients. Current 2022 total program patient census equals approximately 100. Key contemporary programmatic observations relate to the following factors: 1) improvement in survival and reduced mortality, 2) reduction in hospitalizations for acute infectious exacerbations of CF lung disease and 3) marked increase in the number of women successfully completing pregnancy, child-birth and subsequently entering into motherhood

Survival/Mortality

Acknowledging these numerous therapeutic advancements, CF remains at times a fatal disease and CF patients still die from this disease with a total of 68 adult patients dying over the past 20 years at PSH-HMC. However, for historical perspectives note the serial mortality data over the past 20 years since existence of the CFF-accredited adult CF program at PSH-HMC in five-year intervals: 2001-2005 n=9; 2006–2010 n=18; 2011–2015 n= 25; 2016–2020 n= 13; 2021–2022 n=3. The marked reduction in yearly deaths is obvious over the past two years. Although not objectively tabulated, the obvious marked benefits in overall functionality, reduced lung symptomatology and improved quality of life are also clearly evident to all care providers following the availability of CFTR modulator therapies most significantly the triple combination of elexacaftor, tezacaftor, ivacaftor (ETI).

Hospitalizations

In a published abstract presented at the 2014 North American Cystic Fibrosis Conference, we reported that over a 10-month period in 2014, there were 73 individual CF patients admitted and hospitalized secondary to acute infectious exacerbations at PSH-HMC who accounted for 137 total admissions [11]. Since the introduction of triple combination CFTR modulator therapy hospitalization of an adult patient for an acute infectious exacerbation of their existent CF bronchiectasis is uncommon. During 2021 calendar year, there were only 28 hospitalizations for adult CF patients at PSH-HMC. These observations are consistent with data published in the pivotal clinical trial of elexacaftor, tezacaftor, ivacaftor (ETI) that provided the basis for regulatory approval. Treatment with elexacaftor, tezacaftor, ivacaftor (ETI) for 24 weeks resulted in a 63% lower annualized rate of pulmonary exacerbations than placebo (0.25 to 0.55; P<0.001) [10]. A similar benefit was seen with respect to the rate of exacerbations that led to hospitalization (estimated event rate per patient●year 0.07 vs. 0.24) or that were treated with intravenous antibiotics (estimated event rate per patient●year 0.08 vs. 0.36) [10].

Pregnancy/Motherhood

Early descriptions of the reproductive potential of patients with CF often referred to men accurately as sterile due to congenital bilateral absence of the vas deferens (although testicular spermatogenesis and sperm vitality remain normal allowing for the potential use of *in vitro* fertilization) and women as infertile thought to be the result of both hostile cervical mucus and vaginal secretions plus general overall poor health status [12]. Later studies challenged the concept of viscous abnormal cervical secretions detrimental to sperm motility and suggested that the basis for infertility was predominately poor overall health status. Observations and publications in relation to pregnancy potential of women with CF following the initiation of CFTR modulator therapies would indicate that both theories were correct. In 2020 at the PSH-HMC adult CF program there were seven pregnancies with one elective termination and two spontaneous abortions. In 2021 there were also seven pregnancies with two spontaneous abortions. In comparison over the five-year period of time from 2015 – 2020, we are aware of only three pregnancies. These observations are consistent with published data where per information reported in the CFF 2019 patient registry, the number of pregnancies in females with CF in 2009 prior to the first approval of a CFTR modifier (ivacaftor) there were 230 pregnancies,

the number of females with CF becoming pregnant since the advent of CFTR modifiers has since steadily increased with the actual reported number in 2019 equal to 310. One study reported that after commencing highly effective CFTR modulating treatment, 14 spontaneous pregnancies were achieved in 200 women with CF at a median on eight weeks; four had a prior history of infertility and seven were not trying to conceive but used suboptimal contraception [13].

Considerations

This changing clinical landscape for CF patients will require major revisions in current clinical practice patterns and adjustments by all care providers, including the addition of care providers previously minimally involved in CF patient care. Such changes could potentially include:

- Less frequent outpatient evaluations than current recommendations of quarterly or every three months clinic visits and possibly elimination of the standard yearly recommended laboratory, microbiology and radiological assessments;
- Re-indoctrinating hospitalists and internists into the direct inpatient care management of those CF patients requiring hospitalization without relegation to a separate independent CF-specific care team;
- Pending ongoing and upcoming clinical trials, adjustments in lung heath maintenance therapy guidelines will probably be revised to less burdensome treatment regimens;
- Greater outreach will be required beyond just the approximate 100 CFF accredited CF centers in the United States with much broader and locally based community care groups;
- With improvements in overall health status, revisions to the standard definition of an acute exacerbation of lung disease will probably be required with exacerbation defining criteria based more upon physiological parameters such as pulmonary function tests and potentially serum biomarkers rather than the current reliance upon subjective changes in symptoms [14].
- Durations of antibiotic administration outside the usual 10-14 days for acute infectious exacerbations may require modification especially given the fact that the only antibiotic duration study completed to date recruited less than 10% of patients with highly-effective CFTR modifiers and thus lacks any contemporary relevance [14].
- Family planning, pregnancy and motherhood will need to be added high on the list of treatment priority goals as opposed to prior focus upon lung function and survival and will require renewed education plans and the addition of a whole spectrum of care providers not routinely associated with the care of adult CF patients, including genetic counselors;
- Standard routine general health practices such as screening studies, wellness assessments including formal exercise regimens, psychiatric care when advised will now become standards, which will mandate the recruitment of a totally new spectrum of adult CF care providers on a regular and consistent (as opposed to as needed) basis;
- Renewed focuses upon physical, emotional and mental health with employment of standard screening tools to identify psychological stressors and social determinants;
- Nutritionists and dietitians will need to refocus goals not only to avoid malnutrition and weight loss but also just as important to avoid obesity and provide general healthy dietary habits for a much older CF population;
- With improved health status, reduced disability and anticipated increased longevity, there will exist greater opportunities for sustained life-long education, career development and gainful employment which may serve to reduced reliance financially upon medical disability programs and other governmental supplemental income sources.

Conclusion

Finally, primary care providers (PCPs), internists, family medicine physicians and advanced practice providers (APPs) must assume an active primary role in the care of CF patients with the responsibility of the CF specialists restricted to expertise to that disease specifically.

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Authors' Contributions

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Conflict of Interest

Neither author has any conflicts of interest to declare.

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