

## A Modern Era in Approaching Cystic Fibrosis

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Cystic fibrosis (CF) is an autosomal recessive genetic disorder characterized by multi-system manifestations and limited life expectancy. Although it is a multi-system disease its main manifestation is expressed as a progressive chronic lung disease which at the present time accounts for the vast majority of morbidity and mortality. The CF lung disease is chronic and progressive represented by bronchiectasis, recurrent pulmonary infections with tenacious secretions, mucus plugging and gradual decline in lung function. The essence of Cystic Fibrosis is a dysfunctional Cystic Fibrosis Trans membrane Conductance Regulator (CFTR) protein which is deficient or defective. Median life expectancy before 1950 was less than five years, but with the introduction of pancreatic enzymes median life expectancy rose to 10 years by 1960. As anti-staphylococcal antimicrobials were introduced into the care of CF median life expectancy by 1970 was approximately 15 years. In the 1970s anti-pseudomonas regimens were deployed and by 1980 median life expectancy approximated 20 years. In the 1980's and in subsequent years additional aggressive therapeutic regimens targeting primarily the lungs were introduced and they included among others better anti-pseudomonas treatments in oral and intravenous forms but more importantly in inhaled or aerosolized forms. The main prototype of antimicrobial delivered by inhalation was "TOBI" (tobramycin by inhalation). Other important regimens included more effective airway clearance devices, inhaled Pulmozyme (DNase), hypertonic saline, anti-inflammatory agents and the ultimate intervention with lung transplantation for end-stage lung disease. The success in the period between 1980 and 2006 was manifested by improvement in the median life expectancy to approximately 37.5 years. Presently, in 2015, median life expectancy is about 40 years.

A new era in treating CF has emerged in recent years and its noticeable success has been characterized as "the end of the beginning"(1-3). I am referring to treating CF patients with "small molecules" such as Ivacaftor (VX-770) which is a "potentiator" and targets CF patients with the G551D mutation. The success of this approach has been described in a recent publication (4). A newer and most recent therapeutic regimen incorporates the "potentiator" Ivacaftor with the "corrector" Lumacaftor (VX-809) in Cystic Fibrosis patients homozygous for Phe508del CFTR considered to be the most common CFTR mutation. The clinical studies evaluating this combination (VX-770 plus VX-809) provided some benefits to CF patients as demonstrated by improvement in lung function (FEV1%) and reduction in pulmonary exacerbations(5).

While many CF centers are implementing new regimens (1) and as leading centers explore the potential for "gene transfer"

(incorporating a normal gene into CF airway cells) the major issue of dealing with inflammation in the CF lung has not yet been addressed satisfactorily. Chronic inflammation in the CF lung emanates from a variety of cells, primarily neutrophils and in the majority of cases from chronic complex infections. Those play a pivotal role in the gradual process of lung destruction, a direct consequence of chronic inflammation. We have studied the clinical implications of interleukin cytokines on CF lung (6-8). The issue of inflammation which was addressed for the past many years in multicenter studies deploying anti-inflammatory agents has been only partially successful(9). New attempts are underway to study leukotriene modulators utilizing anti-IL monoclonal antibodies (anti-interleukin cytokines antibodies). If successful it will add another important dimension to the "ammunition" against this dreadful disease in the form of anti-inflammatory therapy. Some success with such approach was recently noted in treating difficult asthmatic patients by using monoclonal anti-IL-5 antibody in the form of Mepolizumab (10). An approach similar to that used in severe eosinophilic asthma with frequent exacerbations can certainly be adapted to the CF population where by the common important denominator is inflammation.

Our Cystic Fibrosis Centers for infants, children and adults collaborate with various multicenter studies through the Therapeutic Development Network (TDN) of the Cystic Fibrosis Foundation (CFF) which was instrumental in the success of many landmark studies adhering to its philosophy of collaborative research. Similarly, our specialized pediatric pulmonary centers incorporate clinics for asthma and also treat populations with "difficult asthma", allergy and immune disorders as well as food allergy.

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