EDITORIAL

NEW ADVANCES IN CYSTIC FIBROSIS — IMPLICATIONS FOR DEVELOPING COUNTRIES

There has been substantial progress in the understanding of cystic fibrosis (CF) in the past decade. The discovery of the gene in 1989 provided an important impetus to understanding the molecular basis of CF and its pathogenesis, and offered a means of diagnosing the disease. Perhaps more importantly it broadened our concept of the clinical spectrum of CF and gave rise to new options for treating this potentially devastating disease.

CF is caused by a mutation in a single gene on the long arm of chromosome 7 that encodes the cystic fibrosis transmembrane regulator (CFTR).[1] The basic defect in CF is an alteration in the regulation of ion transport across the apical membranes of epithelial cells. Mutations in the CF gene produce dysfunctional or absent CFTR, resulting in defective chloride and sodium absorption in the respiratory, gastro-intestinal and reproductive tracts.[2] To date over 700 mutations have been reported, the most common of which is the ΔF508 mutation, present in 82% and 53% of CF genes of white (European origin) and coloured (mixed ancestry) South African patients, respectively.[3] This mutation has not been identified in black South Africans, in whom other mutations, such as 3120+1G→A, predominate. This mutation was shown to be present in 4 out of 6 CFTR genes from 3 black CF patients.[4] Studies on the carrier status of healthy black South Africans indicate that CF is likely to be much more common in this population than was formerly recognised.[5] Genotyping has thus afforded a broader view of the extent of CF in the South African population and has improved the accuracy of prenatal diagnosis and genetic counselling. Although the sweat test remains the standard method for diagnosis, genotyping has improved the ability to diagnose CF, particularly when the clinical presentation is atypical or the sweat test normal or equivocal.[6]

Respiratory disease is the primary cause of morbidity and mortality in CF. Lung disease results from two processes — chronic endobronchial infection and neutrophil-dominated airway inflammation. Conventional therapy has focused on clearance of lower airway secretions (using physiotherapy techniques and bronchodilators), antibiotic administration and maintenance of adequate nutrition (using pancreatic enzyme replacements and nutritional supplements). Several new and effective therapies for CF lung disease have been developed.[7] For chronic endobronchial *Pseudomonas aeruginosa* infection, aerosolised antibiotic therapy, particularly the aminoglycosides, has resulted in improved pulmonary function, reduced need for intravenous antibiotics and decreased duration of hospitalisation.[8,9] The development of quinolone antibiotics, principally ciprofloxacin, has offered an effective oral therapy for susceptible *P. aeruginosa*.[10] Anti-inflammatory therapy with ibuprofen may slow the progression of CF lung disease by reducing airway inflammation, particularly when used in young patients with mild disease.[11] Inhaled recombinant human deoxyribonuclease (rhDNase I), a treatment that decreases sputum viscosity by cleaving extracellular DNA originating from inflammatory cells, has reduced the frequency of severe respiratory exacerbations and the annual deterioration in pulmonary function.[12] Recent data suggest that nebulised hypertonic saline may produce similar improvements in lung function, although further confirmation of this is awaited.[13] Lung transplantation, an option for CF patients with end-stage pulmonary disease in some overseas centres, may improve both quality of life and survival.[14] Although this has been performed in South Africa, cost and lack of experience in postoperative care of these patients may limit the success of this procedure.

Potential future therapies for CF lung disease include other anti-inflammatory agents, modulators of ion transport, and gene replacement therapy. Aerosolised anti-proteases such as secretory leucocyte protease inhibitor and α_1-antitrypsin may prevent lung damage resulting from neutrophil elastase. Inhibitors of neutrophil chemotaxis such as pentoxifylline may prevent the influx of neutrophils and the development of florid airway inflammation and lung injury. Activators of alternative chloride channels such as uridine triphosphate, or sodium channel antagonists such as amiloride, may normalise the defect in ion secretion and absorption. Gene therapy in the form of adenoviral vectors and liposomes has been used to deliver the complementary DNA for CFTR into the respiratory tract of adults with CF.[15] Although it appears that the CFTR gene can be transduced into the respiratory epithelium using either of these methods, the clinical benefit, duration of effect, long-term outcome and side-effects of such therapy await full evaluation.

Although the development of new therapies has improved the outlook of patients with CF, the major impact on survival has resulted from the application of standard, conventional treatments given early in the disease. Key factors influencing prognosis include early diagnosis, maintenance of optimal nutrition and aggressive treatment of pulmonary infections. Patients diagnosed and referred to a CF centre before the age of 1 year have better lung function at 14 years than those diagnosed later[16] — timely diagnosis and referral of CF patients is therefore essential. The impact of *P. aeruginosa* infection on lung function is apparent from the accompanying paper by Zar *et al.*,[17] and the benefit of antipseudomonal treatment has been demonstrated in a number of studies.[7-9,18] The ability of the community or patient to afford relatively

costly long-term, lifelong care also impacts directly on outcome. Newer treatments such as rhDNase appear to offer improved outcome, but at considerable additional cost.

The question of what should be considered minimal acceptable treatment of CF in developing countries is an evocative and controversial question. Firstly, the value of a CF centre where a multidisciplinary team including doctors, physiotherapists, nutritionists and social workers can provide support for all the important aspects of this disease must be emphasised. These clinics require co-ordination and a suitable location in large regional centres. Secondly, provision of standard conventional therapy including antibiotics, pancreatic enzyme replacement therapy and nutritional support needs to be assured, as these constitute basic care for CF patients. Thirdly, treatment for CF-associated complications such as diabetes should be provided. It is gratifying to note that the prognosis for South African children, although not as good as for North American patients,[19] has improved significantly with this approach.[20] As a result the majority of CF patients born in 1998 can be expected to survive into adulthood. A consensus document on the care of CF patients is currently being compiled by the medical and scientific advisory committee of the South African Cystic Fibrosis Association (SACFA), and will soon be available.

Assurance of continued lifelong care is a serious concern for all patients with chronic diseases, particularly for those who, like CF sufferers, require a variety of costly drugs. The cost of rhDNase, transplantation, and in time possibly gene therapy place these treatments beyond the reach of State funding, but may be accommodated within the cover of some private medical aid schemes. CF clinics and support groups need to continue their important advocacy role in ensuring continued governmental, medical aid and private support.

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