What you don’t know can hurt you; early asymptomatic lung disease in cystic fibrosis

Steve Cunningham

Clinicians caring for children with cystic fibrosis (CF) should now take note; despite your best clinical care, lung disease in CF infants develops surreptitiously and ill-defined by early symptoms. By the time lung disease has symptomatically declared itself, it’s probably structurally established and too late to reverse. What you don’t know can hurt you.

Hoo and colleagues in this issue provide evidence of early lung disease in patients with CF diagnosed by newborn screening. At a mean 3 months of age, 54% of CF patients had abnormalities of pulmonary function (including lung clearance index (LCI) and/or forced expiratory volume in 0.5 second [FEV$_{0.5}$]) when compared with healthy controls. The presence of symptoms, sometimes aggressively treated, did not reliably identify those with abnormal pulmonary function. This study, by the London CF Collaborative, used contemporaneous healthy controls and adhered to treatment protocols from diagnosis. The research examines with great clarity the vital question of how early lung disease starts in those born with CF. The children studied were provided with every opportunity for optimal health, by the use of newborn screening, regular chest physiotherapy and prophylactic oral fluocxacillin.

Disappointingly, our current best care is not good enough to prevent lung disease. Possibly.

If focal areas of ventilation inhomogeneity change on imaging also needs more investigation. Inevitably CT Chest, readily available, will be the predominant anatomical comparator in such studies, but hyperpolarised helium MRI (HeMRI) may also offer useful insight, as it is able to provide synchronous imaging and quantifiable measure of focal ventilation inhomogeneity.

In a recent interventional study of Ivacaftor, focal areas of ventilation inhomogeneity (assessed by HeMRI) were improved by therapeutic intervention, but the same areas ‘relapsed’ once the intervention was terminated. If focal areas of ventilation inhomogeneity become chronically susceptible to injury, then early intervention trials to prevent such change may be critical to avert early CF lung disease. As a technology, HeMRI has constrained application in the clinical context, so the ability of MBW LCI to sensitively and specifically identify ventilation defects detected by HeMRI warrants further research.

To prevent early CF lung disease, bronchiectasis and ventilation inhomogeneity, as surrogate biomarkers should be made primary outcomes in clinical research studies. To become primary outcomes, surrogate biomarkers require to be approved by regulatory authorities and adopted by pharmaceutical companies for phase III clinical trials. The sensitivity of CT chest and ventilation inhomogeneity to early lung disease in CF has been recognised in recent US NHLBI workshop and European Respiratory Society Research Seminar (Rotterdam, March 2012). Both Cts and MBW LCI were identified as critical areas for further development and standardisation, to enable their use as primary outcomes in multicentre interventional studies. The CF research community is growing in confidence to challenge and support both regulators and pharmaceutical companies to make more effective assessments of potential therapies using these novel surrogate biomarkers. This is particularly pressing for infants and preschool children where current regulatory requirements may be considered insufficiently demanding of patient benefit. In response, regulators will request that

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In children under 5 years treated with nebulised hypertonic saline as part of the ISIS trial, while the primary outcome for the trial was negative, measures of forced expiratory flow demonstrated significant improvement in the subset of patients tested, suggesting that more sensitive measures may be able to demonstrate effectiveness of therapies when studying younger children.

The association between changes in ventilation inhomogeneity and structural change on imaging also needs more investigation.
proposed novel surrogate biomarkers are exposed to appropriate levels of critical scrutiny: demonstrated to be safe, quantifiable and reproducible, sensitive to meaningful changes in patient health, and reflect relevant clinical patient benefit.

Several CF interventional clinical studies have now reported CT chest and LCI as trial endpoints, supporting the case that these novel surrogate biomarkers can be sensitive and meaningful measures of patient health. Treatment of a respiratory exacerbation in CF children at mean age of 3 years with a course of intravenous antibiotics and intensive chest physiotherapy is associated with an improvement in chest CT scores, particularly bronchial dilation/bronchiectasis. Further evidence that novel pulmonary function measures (LCI) may provide a more sensitive signal of therapeutic benefit has recently been reported in three studies where patients receiving the intervention had normal lung function. Statistically significant improvements in LCI over placebo was demonstrated for hypertonic saline, and ivacaftor in G551D patients. Systematic amalgamation of current evidence, supported by unpublished standardisation data, should enable these biomarkers to enter routine use in CF clinical trials. The entrance will be timely; multiple novel agents are in Phase II and III trials, and could benefit from more sensitive markers of effect for pharmacological intervention of cystic fibrosis transmembrane regulator (CFTR) malfunction (UK CF Gene Therapy Multidose Trial, Vertex Pharmaceutical interventions for Class II and IV mutations, and Class III mutations in young children, PTC Therapeutics for Class I mutations).

Clinicians increasingly understand how much they must strive to deliver their patients to the point of future pharmacogenetic correction with no, or limited, lung damage. The report by Lum and colleagues adds clinical pressure at an earlier age. But, how can we do this, if we can’t see it, can’t hear it and can’t routinely measure it? In this age of enlightenment to the dangers of early CF lung disease, early intervention trials with appropriately approved biomarkers hold the key.

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