Pulmonary exacerbations as indicators of progression of lung disease in young children with CF

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The approval of ivacaftor by the European Medicines Agency (EMA) and the US Food and Drug Administration (US FDA) and the ongoing development of other drugs that target the underlying defect that causes cystic fibrosis (CF) have generated a great deal of excitement and hope for patients with CF.[1 2] To truly maximise the potential benefits of these drugs, they will need to be administered before irreversible lung disease (eg, bronchiectasis) develops. Most patients with CF who have taken part in therapeutic drug trials have been at least 6 years of age, when most patients begin to be able to perform spirometry, the most commonly used endpoint in CF therapeutic trials. However, an observational study in Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) demonstrated that structural lung disease, including bronchiectasis, may be present even in infancy.[3] Thus, to minimise the progression of lung disease, we must initiate treatment as early as safely possible for those patients who are at risk for developing lung disease. The challenge in obtaining EMA or FDA approval for new therapeutic interventions to be administered in early life, where the progression of lung disease occurs in a 'black box', is demonstrating safety and efficacy in children too young to perform traditional spirometry. Given that pulmonary exacerbations occur frequently even in young children, they offer an inviting clinical endpoint for future studies in this age group. The FDA defines clinical endpoints as direct measures of how a patient feels, functions or survives.[4] Pulmonary exacerbations are clinically meaningful endpoints that are associated with survival,[5] future deterioration of spirometry[6] and increased bronchiectasis,[7] consume significant clinical resources[8] and impact quality of life[9] in studies of older children and adults.

Byrnes *et al*[10] add strength to the argument that pulmonary exacerbations can be a meaningful clinical endpoint for young children. They demonstrated that there are associations between frequent pulmonary exacerbations, especially in the first 2 years of life, and decreased spirometry (FEV_1) at age 5, and between more frequent pulmonary exacerbations treated with intravenous antibiotics and the presence of bronchiectasis on chest CT and decreased weight for age at age 5. The study enrolled children with CF before 6 months of age after being identified via newborn screening. The original studies of the risks and benefits of new born screening (NBS) for CF failed to demonstrate an improvement in pulmonary outcomes as children reached adolescence.[11] This study clearly highlights an opportunity provided by NBS (ie, to identify and appropriately treat pulmonary exacerbations in the first few years of life) to improve long-term pulmonary outcomes.

One of the challenges with pulmonary exacerbations in this age group is that they might merely represent stochastic events related to viral infections that might not be preventable. The authors point out that the frequency of pulmonary exacerbations is somewhat similar to the frequency of viral upper respiratory tract infections that occur in healthy children without CF.[12] We know that children with CF are more likely to have prolonged viral infections and of greater severity.[13] The presence of rhinovirus[14] and respiratory syncytial virus[15] may enable *Pseudomonas* to more easily infect airway epithelial cells from patients with CF. Of concern, the recent Infant Study of Inhaled Saline (ISIS) in CF study found that inhaled hypertonic saline failed to decrease the rate of pulmonary exacerbations in children aged 4–60 months with CF using an alternative definition.[16] Was the definition wrong, or do we need a number of endpoints to assess treatment benefit in small children? Studies of disease-modifying drugs will clearly not only need to evaluate pulmonary exacerbations as an endpoint in this age group but also look to other outcome measures to ensure success. In the ISIS study, a subgroup of patients performed infant pulmonary function testing, and

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patients who received inhaled hypertonic saline had a significantly larger mean improvement in forced expiratory volume in 0.5 s.[16] Serial chest CT scans have demonstrated structural lung disease, such as bronchiectasis, that is persistent and progressive even in young children with CF.[17] The primary endpoint of an ongoing study of azithromycin for young children with CF is the prevention of bronchiectasis on chest CT at age 3.[18] Additionally, the lung clearance index (LCI), an outcome measure using the multiple-breath washout (MBW) method, has been shown to be repeatable, reproducible and sensitive in detecting the presence of lung disease in children with CF as young as 4 months of age.[19] LCI in 3–5-year-olds with CF is predictive of future LCI at 6–10 years of age.[20] It should be noted that neither infant pulmonary function testing nor LCI have been validated as endpoints by either the EMA or the FDA.

Many questions remain regarding pulmonary exacerbations in young children with CF. Do frequent (viral) pulmonary exacerbations lead to global obstructive lung disease and result in lower FEV_1 at age 5, whereas more significant (presumably bacterial) pulmonary exacerbations that lead a clinician to treat with intravenous antibiotics lead to focal injury (bronchiectasis)? In that case, should antibiotic prophylaxis be used, since lower pulmonary exacerbation rates were found in areas that used prophylaxis, and does that make up for the potential risks of earlier *Pseudomonas aeruginosa* acquisition seen in children with CF who receive antibiotic prophylaxis?[21] Or is it that patients who already have bronchiectasis are more likely to require intravenous antibiotics for treatment? Baseline chest imaging was not available in this cohort, although the AREST-CF study would indicate that at least some of these patients had bronchiectasis early on.[3] It is not known if the rate of pulmonary exacerbations can be reduced in this age group through other therapeutic interventions. The ISIS study showed that hypertonic saline could not reduce the rate of pulmonary exacerbations in infants with CF.[16] Similar studies of other therapies approved for older children and adults with CF (eg, azithromycin, dornase α, inhaled tobramycin) have not been conducted. Finally, without spirometry, it is difficult to assess whether young children ultimately recover following pulmonary exacerbations.[22]

There have long been calls for a standard definition of a pulmonary exacerbation. Such a definition cannot work for all age groups. Clearly for small children, using a wide net to define an exacerbation was meaningful; patients experiencing these events went on to have lower FEV_1, weight for age and/or more bronchiectasis. To satisfy regulatory agencies' definition of clinically meaningful endpoints, additional patient (parent)-reported outcomes may need to be included in any definition of pulmonary exacerbation.[23] A standard pulmonary exacerbation definition for this age group is necessary, at least in order to easily compare results between different studies. In the meantime, it would seem that, at least for young children with CF, more aggressive therapy may be indicated, even for symptoms that may be due 'only' to a viral infection. While there are many important questions that need to be addressed, the current report has begun to open the 'black box' to enable us to monitor the progression of CF lung disease in young children.

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