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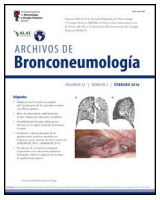

Editorial

# Cystic Fibrosis: From Salty Malediction to Possible Cure


"I feel like a normal person", "I will be able to have children and see them grow up", "I will be able to live a life with a long-term future", are expressions that translate the effect that the triple Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulator therapy has produced on people with cystic fibrosis (pwCF) who are eligible for this treatment.

From its approval by the US Food and Drug Administration in 2019 to the present day, the triple CFTR modulator therapy (elexacaftor for Phe508del mutation to the present, tezacaftor and ivacaftor [ETI]) has produced a paradigm shift in the management of CF. The clinical trials that supported their approval,[1–3] as well as subsequent real-life studies,[4–7] have provided efficacy, effectiveness and safety. Consequently, treatment with ETI together with the traditional therapeutic approach has significantly improved the morbidity and survival of these patients.[8] When it was initially described, the disease carried a very high infant mortality; nowadays, pwCF reach adulthood, and patients eligible for ETI have a hopeful future.

The clinical impact of ETI has led to changes in the management of CF and, at the same time, a challenge for healthcare systems. In Spain, treatment with ETI is approved from the age of 6 years and the trend is to start it as early as possible to avoid the development of irreversible airway damage; there is also some evidence supporting an early life window for pancreatic disease. It is estimated that the number of treatable patients is over 70% in Spain and reaches 90–95% in northern Europe and the USA.[9,10]

Currently, a demographic shift towards an increasing proportion of adult CF patients is evident since 2015. There is a larger adult than paediatric population[10] and it is foreseeable that this gap will increase over time. In addition, the projected models of for pwCF commenced on ETI from adolescence (12–17 years) estimate survival of up to 82 years. For the same patients without ETI, median predicted survival is currently around 40 years.[8] These benefits of ETI have given rise to two emerging phenomena in the CF world: an increase in pregnancy rates and a dramatic decrease in the numbers of lung transplants procedures. Lung transplantation for CF aetiology decreased by 85% after 3 years of treatment with ETI in USA.[10]

The demographic change will clearly affect the organisation of multidisciplinary teams (MDT) and CF care. MDTs face a requirement for new competencies and therapeutic challenges such as pregnancy, breastfeeding, metabolic complications, diseases associated with ageing, psycho-affective disorders and issues arising from pwCF entering the labour market in greater numbers. We may see a community with a milder lung disease, issues relating to overweight such as a higher risk of metabolic syndrome.[10] This new reality translates into at least three current controversies for the CF care.

First, there are changes in how perform disease monitoring. Treatment with ETI markedly decreases sputum production to the point that many patients report being 'dry'. Whilst welcome for pwCF, a lack of respiratory samples available for analysis raises a challenge for the surveillance of bronchial infection. Consequently, several studies have analysed different procedures to detect infection, with induced sputum emerging as good alternative method with comparable results to bronchoalveolar lavage.[11] It is however time-consuming and burdensome for the pwCF and the MDT. There is also a clinical challenge in the assessment of earlier-stage/milder lung disease and its progression. It is likely that traditional respiratory function tests (spirometry) will be replaced by other, more accurate and sensitive methods such as the lung clearance index[12] or magnetic resonance imaging.[13]

Currently, most of the treatment burden in CF relates to physical therapy, secretion management with mucoactive nebulisers and chronic inhaled antibiotics. The clinical and functional improvement produced by ETI, raises the second challenging question of whether it is necessary maintain the same burdensome treatment once ETI is commence as sputum is greatly reduced and has different characteristics. The SIMPLFY study,[14] addressing this topic, concluded that pwCF undergoing ETI and well-preserved lung function, can discontinue hypertonic saline or dornase alfa with no impact on lung function tests. In real life, patients are stopping these treatments with the same result, no changes in lung function. However, most patients in SIMPLFY had mild/moderate lung disease; although this might be acceptable for patients with well-preserved lung function, it may not apply for those with more advance disease. In these cases, the patient may have a false sense of being well as pulmonary exacerbations are not perceived with the same intensity, but their clinical impact on CF prognosis could be similar; further evidence is needed before mucoactive treatments are stopped. Moreover, SIMPLFY was a short study with only 6-week randomised treatment arms. The HERO-2[15] and CF-STORM real-life trials will provide further insight into the longer-term consequences of discontinuing medication and treatments while taking ETI. Other adherence challenge is to ETI itself, perhaps particularly in young people who have never experienced symptoms and feel healthy.

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On the other hand, ETI is not currently licensed post lung transplantation; an unmet research need is to establish whether transplanted patients could gain benefits outside the lower airway.

Thirdly, and as a consequence of everything described above, treatment with ETI will force a change in the healthcare model. Now, patients on ETI require fewer intravenous antibiotic cycles and hospitalizations. This is leading mostly to an outpatient model of CF care. In-person outpatient visits are decreasing and possibly the use of telemedicine will become more frequent mainly in stable patients. This change in CF care, whilst welcome to many, will require the development of new care guidelines that consider patients with and without ETI. Physicians should keep in mind that a percentage of around 8% will be at risk of developing severe disease, and in some countries such as Spain, up to 30% of pwCF are not eligible for ETI. That means that different CF patient profiles are coexisting and therefore a continuous training of the MDT is needed. ETI treatment is not the cure of the disease and that there are still mutations without effective treatment. ETI is currently being studied in other mutations and there are other drugs in development for nonsense mutations, splice and framework mutations and deletions or duplications of exons.[16]

In conclusion, it is a time of hope but with many changes and doubts. CF has not been cured yet, but it is becoming a different disease, requiring adaptation of the multidisciplinary team and health care systems. New topics such as complications of ageing, mental health, pregnancy, management of adverse effects or indication for transplantation urgently need to be addressed. Improved health will probably mean increasing implementation of telemedicine and a need for less specialised care networks for a high percentage of CF patients. However, there are and will remain patients with classic disease, ineligible for ETI, with advanced disease, post-liver or lung transplant, or non-responders to ETI. CF units should modify care pathways, with new guidelines shortly.

Working together, the CF community has made truly unprecedented progress, but celebration of this leaves no room for complacency; we need to continue in our endeavours to ensure all patients have access to therapies targeting the underlying CFTR defect and embrace the evolving models of clinical care required to care for people living their lives with cystic fibrosis.

## Conflict of interests

The authors state that they have no conflict of interests.

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