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Azithromycin for primary ciliary dyskinesia: a milestone

Primary Ciliary Dyskinesia (PCD) is a rare disease of motile cilia dysfunction, with wide genetic heterogeneity and clinical variability. The hallmark of the disorder is the impairment of muco-ciliary clearance, which results in recurrent airways infections, development of bronchiectasis, and progressive pulmonary function worsening.[1]

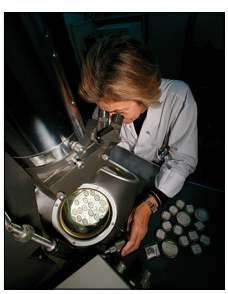
The European Respiratory Society and American Thoracic Society have separately developed PCD guidelines focused on diagnostic work-up, with some differences between the two guidelines.[2] Indeed, due to the fact that there are only a few controlled clinical trials, PCD lung disease-specific and evidence-based recommendations on treatment are missing. In current daily practice, preventive and therapeutic strategies for PCD are extrapolated from other chronic respiratory disorders, mainly cystic fibrosis and non-cystic fibrosis bronchiectasis, without a shared approach among centres.[3] Moreover, as the pathophysiology of mucociliary abnormalities in PCD is probably different from other disorders, namely cystic fibrosis, adopting PCD treatments from similar conditions is questionable. Therefore, more trials are urgently needed to specifically address management of PCD.

In *The Lancet Respiratory Medicine*, Helene Kobbernagel and colleagues[4] report the results of the BESTCILIA multicentre phase 3 trial of 90 patients with PCD who were randomly assigned to azithromycin treatment three times a week or placebo for a 6-months period. Their aim was to define the efficacy of prolonged azithromycin treatment in reducing the number of respiratory exacerbations.

Why did authors choose to investigate macrolides? The answer is that those antibiotics, in addition to well known bacteriostatic properties, have anti-inflammatory and immunomodulatory effects. Macrolides are effective against biofilm growth by quorum sensing inhibition, and thus reduce the risk of growth of *Pseudomonas aeruginosa* and other pathogens. The first evidence of prolonged macrolide use for respiratory conditions dates back to 1998, when erythromycin maintenance therapy in diffuse panbronchiolitis was associated with a dramatic improvement in mortality.[5] Since then, many studies on long-term macrolide treatment have been carried out in chronic respiratory suppurative diseases. Best results in terms of reduced exacerbations and improved lung function were reported in cystic fibrosis and non-cystic fibrosis bronchiectasis.[6]

With this background in mind, the BESTCILIA trial[4] appears to be a milestone that confirms and extends to PCD the data from other chronic lung disorders. The main findings of the study were a significantly lower number of exacerbations (rate ratio 0·45, 95% CI 0·26–0·78; p=0·004) and mean number of pathogenic airway bacterial species (mean difference 1·47, 95% CI 0·65–2·30; p=0·0007) in patients in the azithromycin group compared with placebo. The study has many strengths, including the randomisation, the allocation to a placebo group, and a wide age range of participants from childhood to adulthood. Authors also evaluated PCD-specific quality of life and multiple breath washout, which, although unchanged, are key outcome measures in clinical trials. A limitation is the risk of adverse effects of azithromycin, which might have led to drop-outs, and the possible increase in macrolide-resistant bacteria. However, the availability of several different classes of antibiotics and the possibility of using them effectively in exacerbations could overcome this drawback.

The whole PCD community, including paediatric and adult specialists, chest therapists, and patients and their families will welcome the BESTCILIA results. No orphan drugs are currently available for PCD. Nevertheless, specific genotypes have been associated with a severe respiratory PCD phenotype.[7] The identification, on the basis of genetics, of which patients would most benefit from macrolides will be of considerable importance, and is in line with the precision medicine principles for care management of rare diseases.[8]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