Access to medicines for rare diseases: beating the drum for primary ciliary dyskinesia

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Primary ciliary dyskinesia, a rare disease causing bronchiectasis, lacks a sound evidence base for treatment. @beatpcd proposes 1) forming a PCD European clinical trial network to address this situation and 2) conducting n-of-1 trials to access medication. https://bit.ly/3j5blfM

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Rare diseases are collectively common, affecting an estimated 6.2% of the world's population [1], but each rare disease affects fewer than 4 to 5 in 10 000 individuals in Europe or less than 200 000 individuals in the USA [2]. Patients with rare diseases are often disadvantaged by late diagnosis and off-label prescribing of medicines [3]. Primary ciliary dyskinesia (PCD) is a genetic disease of impaired motile ciliary function that does not have a unique International Classification of Diseases (ICD)-10 code or licensed treatments, although Q34.8 denoting "other specified malformations of the respiratory tract" including nasopharyngeal atresia has also been applicable to PCD since 2017. The disease is characterised by mucus stagnation leading to chronic airway infection, bronchiectasis, chronic rhinosinusitis, reduced fertility and abnormalities of organ laterality with an associated increased risk of complex congenital heart disease [4]. The estimated prevalence of PCD in Europe is around 1 in 10 000 to 1 in 20 000 [5]. The international PCD cohort (iPCD) includes over 3800 PCD patients ranging in age from under 12 months to over 80 years, from Europe, Northern and Southern America, Australia and Western Asia [6]. Under-diagnosis of PCD is due to a lack of awareness among the general public and physicians in general, as well as a lack of diagnostic expertise in some countries [7]. Tools to help physicians identify patients needing testing (*e.g.* PICADAR) [8] and the European Respiratory Society (ERS) guidelines for diagnostic testing [9] aim to improve this. In contrast to cystic fibrosis (CF), a monogenic disease, PCD is caused by mutations in one of at least 45 identified genes for which there is no effective mutation-specific therapy; this is likely to be a long way off for most patients [10]. Thus, treatment aims to prevent and manage disease complications. Even then, the lack of an evidence base for supportive treatment in PCD means that treatment recommendations are based on expert opinion and extrapolated from CF despite differing pathophysiology [11].

There are only two published double-blind, randomised, controlled treatment studies in PCD, each a milestone achievement given recruitment difficulties [12, 13]. Paucity of evidence means that patients are exposed to risks including inappropriate dosing [14], deleterious side-effects [15] and increased treatment burden with ineffective therapies. A further consequence has been varying reimbursement policies for medicines, restricting access to inhaled antibiotics for example, with some countries resorting to cheaper alternatives with an inferior safety profile [16] and others displaying regional policy differences [17]. This restriction of access to medicines and the difficulty in conducting clinical trials in PCD is particularly concerning in regard to children. In this editorial, we show how PCD patients are being discriminated against by inequalities of access to medications and propose two solutions. The long-term solution is conducting more randomised controlled trials (RCTs) by the formation of a clinical trials network similar to the existing European and American CF Clinical Trials Networks (ECFS-CTN, CFF-CTN, respectively). Further, the empowerment of and engagement with patient organisations is fundamental to patient recruitment for clinical trials and should be prioritised. The second solution, which can end this discrimination by being implemented immediately, is to allow the prescription of inhaled medications to PCD patients if benefit is demonstrated in an appropriate n-of-1 trial.

Treatment evidence

PCD lung disease is not trivial. Lung function is below 80% predicted in one-third of children at diagnosis [18] and is impaired to a similar degree in childhood compared with CF [19]. A third of paediatric and adult patients will lose more than 10 percentage points of lung function over a 10-year period [18]. Data from the American bronchiectasis registry show that adults with PCD have worse lung function, greater morbidity and are more likely to be infected with *Pseudomonas aeruginosa* than adults with idiopathic bronchiectasis, common variable immunodeficiency and alpha-1 antitrypsin deficiency [20]. Mobilisation of airway secretions is the cornerstone of PCD management [11]. Airway mucus in PCD and CF share similar biophysical properties [21]. The first ever prospective controlled trial of treatment in PCD, a randomised, double-blind cross-over trial of 3 months' treatment with nebulised 7% hypertonic saline (HS) and 0.9% saline, measured quality of life (QoL) and lung function in 22 adults with PCD, finding a significant difference favouring HS only in perception of health [12]. The small number of patients, a result of recruitment difficulty, meant that the study wasn't sufficiently powered to detect differences in the primary outcome measures. An unintended consequence of these negative findings has been the refusal of some insurance companies in the USA to fund HS and nebulisers for PCD patients (M. Leigh, personal communication); payment for HS is not reimbursed in several European countries, a situation remedied by some hospital pharmacies producing their own HS.

Compared with placebo, treatment with inhaled recombinant human deoxyribonuclease (rhDNase) for longer than 6 months is associated with a decrease in pulmonary exacerbations and an improvement in lung function in CF patients [22]. There have been anecdotal reports of improved sputum expectoration and lung function after short- and longer-term treatment with rhDNase in four children with PCD who were deteriorating [23–25]. Conversely, studies of rhDNase in adults with non-CF bronchiectasis showed no clinical benefits in one study [26] and increased frequency of pulmonary exacerbations with worsened

lung function in another [15]. While rhDNase on an individual trial basis can be used when lung function is deteriorating despite maximal medical therapy [27], the prohibitive cost precludes its use in most European countries where the patient must pay. Looking to the future, a more affordable rhDNase (biosimilar JHL 1922) has undergone a phase 1 clinical trial in the Netherlands [28]; a phase 3 trial in CF patients is planned. Such clinical research initiatives represent an opportunity that should be actively pursued by the PCD community.

PCD lung disease is characterised by repeated pulmonary exacerbations. The newly published, multicentre, double-blind, randomised placebo-controlled study, BESTCILIA, showed that thrice weekly maintenance treatment with azithromycin for 6 months in 90 children and adults halved the rate of respiratory exacerbations and significantly reduced the rate of sputum carriage of pathogenic bacteria compared with placebo [13]. This milestone study confirms and extends to PCD data from studies in CF and bronchiectasis, and paves the way for the development of precision medicine approaches for PCD to determine who would most benefit from this treatment [29]. Furthermore, *P. aeruginosa* infection in PCD is common; infection rates as high as 37% have been reported in children [30], and in 39% and 51% of adolescents and adults, respectively [31]. This compares, in the latter two age groups, with 12% and 26% for bronchiectasis and 60% and 67% for CF [31]. Data from the American adult bronchiectasis registry showed a 63.5% prevalence of at least one positive *P. aeruginosa* sputum culture in the previous year [20]. Chronic *P. aeruginosa* infection in PCD is also associated with poorer lung function, especially in women [32], while the impact on life expectancy is unknown. Prompt *P. aeruginosa* eradication is recommended in PCD, but with no evidence to support dosing strategies or duration of treatment [11, 27]. A survey of eradication strategies in European PCD centres showed that in some countries (Belgium, Bulgaria, Turkey and Ukraine), inhaled anti-*P. aeruginosa* antibiotics are not generally prescribed due to lack of reimbursement of costs [16], leaving the patient with either the risk of becoming chronically infected or having to pay, which is prohibitively expensive for most, or being falsely reclassified as having CF.

Proposal

CF is the only chronic suppurative lung disease for which treatment with inhaled antibiotics and rhDNase has been approved by the European Medicines Agency and the US Food and Drug Administration. The five key criteria for reimbursement of medicines in countries within Europe are demonstration of therapeutic benefit, medical necessity, safety, cost-effectiveness and budget impact [33]. Further, reimbursement may be product-specific, disease-specific, population groups-specific (*e.g.* children or pensioners), or consumption based. Demonstration of fulfilment of these five criteria is currently impossible for any inhaled PCD treatments. Given that a cure for PCD is unlikely in the foreseeable future, efforts also need to be directed towards establishing the efficacy in PCD of medicines shown to be effective in treating other causes of bronchiectasis. The BESTCILIA azithromycin study represents an important first step towards this goal and demonstrates the ability of the PCD community to come together to perform RCTs. A formal clinical trials network might be along the lines of the European CF Society Clinical Trial Network (ECFS-CTN) and the CF Foundation Clinical Trial Network (CFF-CTN), ideally involving every diagnosed patient. As soon as one study is completed and the results analysed, the next study should begin. This method, of including virtually every patient in a clinical study, has been adopted for decades in rare childhood cancers, where it has led to impressive improvements in long-term outcomes [34]. BEAT-PCD has recently been granted an ERS Clinical Research Collaboration to advance clinical and translational research in PCD and setting the framework for the formation of a PCD-CTN would fall within this remit. However, clinical trials take time and while they are the gold-standard, it is unreasonable that patients should be denied treatment pending the outcome of such trials. We urge regulatory authorities to fund inhaled medications if they show benefit in the individual patient in an appropriately conducted, n-of-1 trial. It is simply not good enough to refuse to fund because ”there is no evidence”. Absence of evidence should not be interpreted as absence of benefit. Even within RCTs, there is usually a wide range of individual responses, and in clinical practice, an individualised approach is taken when planning therapy. In summary, we, as a group of experts managing the care of PCD patients in Europe and the USA, wish to highlight the discrimination experienced by PCD patients, the likely detrimental effects on exacerbation frequency, future lung function, QoL and healthcare costs, and propose a solution which can be implemented now while on the road to conducting more RCTs.

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