Concept sheet for publication

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Observational Study of Respiratory Exacerbations in Primary Ciliary Dyskinesia (PCD)

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Other Possible participating partners:

- All ERN-LUNG (European reference network) members and affiliated or supporting partners

Authorship suggestion:

Data providers and departments involved in the study will be offered a co-authorship according to the **criteria of the International Committee of Medical Journal Editors**, which include all the following:

i) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work;
ii) drafting the work or revising it critically for important intellectual content;
iii) final approval of the version to be published; and
iv) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Participating centres are offered a maximum of three co-authorships (1: > 10 PCD patients; 2: > 20 PCD patients; 3: > 40 PCD patients) among investigators. All other partners and collaborators contributing to this trial shall be duly acknowledged in the publication.

Background

Pulmonary exacerbations are a cause of significant morbidity in patients with PCD and their frequency and variability can be important clinical outcome measures in prospective clinical research trials. Two different consensuses on the definition of pulmonary exacerbations in PCD have been published recently. One developed through a Delphi process by a multidisciplinary experts and patients *(Lucas JS, et al. ERJ open research 2019)* and another that has been used in the BESTCILIA azithromycin clinical trial *(Kobbernagel HE, et al. BMC Pulmonary Medicine 2016)*. To date there has been no reference to the association of upper airway exacerbations with pulmonary exacerbations in PCD. Therefore, there is a need to assess in prospective observational studies pulmonary exacerbations in PCD, validate the proposed definitions and their inter-relations with upper airway manifestations.

Specific Aims

i) Assess the incidence of upper and lower respiratory exacerbations in PCD over 12 months by age group, gender and chronic pseudomonas colonization status.

ii) Compare the incidence of respiratory exacerbations in PCD as defined by the recently published consensus definition of pulmonary exacerbations (*Lucas JS, et al. ERJ open research 2019*) against the BESTCILIA azithromycin clinical study definition (*Kobbernagel HE, et al. BMC Pulmonary Medicine 2016*).

iii) Assess the variability of individual clinical manifestations relating to respiratory exacerbations over 12 months by age group, gender and chronic pseudomonas colonization status.

Methods

Study design and sample size:

Prospective, 12-month, multicentre, observational study. A priori power analysis (for mean comparisons between independent groups) demonstrates that the required sample size is n=105 per sample group (assumptions: medium effect size, a=0.05, power=0.95). A priori power analysis (for difference between matched pairs) demonstrates that required sample size is n=54 (assumptions: medium effect size, a=0.05, power=0.95)

Inclusion criteria:

i) PCD patients with a positive (hallmark TEM defect or biallelic mutations in PCD causing genes) or highly likely diagnosis (very low nNO plus HSVA findings consistently suggestive of PCD on three occasions or following cell culture) according to European Respiratory Society guidelines (*Lucas JS, et al. European Respiratory Journal 2017*)

ii) Patients (or their guardians) willing to participate in monthly telephone interviews over a period of 12 months. Those who agree to participate will sign a written informed consent according to national legislation requirements

Data Collection:

Monthly telephone interviews with the patients or guardians will be carried out over a period of 12 months. Each telephone interview will review at first the patient's general health over the previous month according to their own views (in patients >12 years). In patients <12 years the views of their caregiver will be sought. More specifically, patients will be specifically asked "How many exacerbations of your disease have you had in the last month? By this I mean infections, bad attacks of your chest / worsening of your symptoms". The question for children <12 years will be "How many exacerbations of your child's disease have you noticed in the last month? By this I mean infections, bad attacks of his/her chest / worsening of his/her symptoms".

Then the interview will focus on the clinical manifestations included in the criteria of the consensus on pulmonary exacerbations (including any intake of antibiotics), but also on other systems manifestations such as nasal secretions and stuffiness (e.g. SNOT-22), earache, tinnitus, reduced hearing and headaches. Patients will be also asked to report any unscheduled visits to physicians or hospitals relating to the above manifestations. Participants may be asked to keep a diary of their key manifestations to help recall during interviews.

In parallel, routine clinical data or emergency hospital visits data collected for the ERN prospective registry such as spirometry, BMI, sputum culture bacteriology will be gathered for each participant and used in the analysis as described below.

Statistical Analysis

i) The frequency of PCD pulmonary exacerbations, as defined by the recently published consensus statement and the BESTCILIA azithromycin clinical study definition, will be assessed over 12 months in all patients.

a. We will compare the differences in the capture of exacerbation events by the two definitions and examine the agreement of each of the two definitions with the self-reported exacerbations. The assessment of the agreement between the different definitions of exacerbations will be carried out using the Cohen's kappa statistic.
b. We will also compare the mean exacerbation frequency by each definition in different groups of patients as defined by:

   i. Age group (children vs adults and pre-school Vs school age children)
   ii. Gender (males Vs females)
   iii. Pseudomonas colonization or not
   iv. Lung function (categorical grouping)

   Unadjusted comparisons will be carried out using Analysis of Variance-ANOVA. Adjusted comparisons will be carried out using General Linear Model (Analysis of Covariance - ANCOVA) to control for the effect of the other covariates in each occasion (i.e age, gender, Pseudomonas colonization status).

ii) We will also explore the variability over time of the collected clinical manifestations, antibiotics usage and emergency visits as individual parameters. The mean frequency of each of these clinical parameters will be compared in the different groups of patients (age group, gender, pseudomonas colonization, lung function) as described above in unadjusted and adjusted analyses.

iii) Finally, we will also assess the association of the two definitions (published consensus statement definition and the BESTCILIA azithromycin clinical study definition) with other systems manifestations such as nasal secretions and stuffiness (e.g. SNOT-22), earache, tinnitus, reduced hearing and headaches. A mixed effects regression model to account for individual subject factors, will be used for statistical analysis.

Ethical Considerations

Each participating center will apply national legislation and obtain Ethics Committee approvals accordingly.

Data safety and data handling

The anonymized and standardized dataset from each trial site will be completed in REDCap, a secure web platform for building and managing online databases using established ERN-LUNG data safety measures.

Target Journal(s):

American Journal of Respiratory and Critical Care Medicine, Lancet Respiratory Medicine, Thorax, European Respiratory Journal, Chest

Milestones:

- 31 March 2020: Finalization of the participating centers
- 30 April 2020: Finalization of translation and back translation of the questionnaire in national languages
- May - June 2020: Bioethical approvals of the study according to national legislations
- June - September 2020: Start of recruitment - data collection
- December 2020: End of recruitment
- December 2021: End of data collection
- June 2022: Analysis of data and first draft manuscript ready

References

1. Lucas, J.S., Gahleitner, F., Amorim, A., et al, 2019. Pulmonary exacerbations in patients with primary ciliary dyskinesia: an expert consensus definition for use in clinical trials. *ERJ open research*, *5*(1), pp.00147-2018.

2. Kobbernagel, H.E., Buchvald, F.F., Haarman, E.G., et al, C., 2016. Study protocol, rationale and recruitment in a European multi-centre randomized controlled trial to determine the efficacy and safety of azithromycin maintenance therapy for 6 months in primary ciliary dyskinesia. BMC pulmonary medicine, 16(1), p.104.

3. Lucas, J.S., Barbato, A., Collins, S.A., et al, 2017. European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. *European Respiratory Journal*, *49*(1).