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Early View

Research letter

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Are inhaled corticosteroids prescribed rationally in primary ciliary dyskinesia?

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Take home message (120 characters): ICS are prescribed irrationally in PCD because diagnosing airway eosinophilia and asthma in this setting is difficult

Primary ciliary dyskinesia (PCD) is a chronic suppurative lung disease, characterised by abnormal mucociliary clearance due to genetic defects of motile cilia. PCD patients often present with wheeze and many are prescribed inhaled corticosteroids (ICS). However, ICS are not recommended by International treatment guidelines unless patients have co-existing asthma or airway reactivity [1], or asthma/wheeze with reversible bronchial obstruction (BDR) [2]. The aim of this cross-sectional single-centre study was to determine whether ICS prescriptions were targeted appropriately in PCD [3].

Ninety-nine children with confirmed PCD [4] were included in this study (52 girls, mean age 9.9±4.7 years), which was performed as a clinical audit project (Royal Brompton Clinical Audit and Service Development, #000979). Sample size was opportunistic as there were no data to inform a power calculation. Statistical analysis was performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com) using Mann-Whitney U test for continuous variables and Fisher's exact test for nominal variables. A p-value <0.05 was considered significant.

We identified patients who were prescribed ICS based on clinic letters at their latest annual assessment between 2014 and 2016 and compared them to the non-ICS control group; we could not define duration of, or adherence to, treatment, and we did not attempt to define treatment response as no formal trials had been done. We retrieved contemporaneous demographic, diagnostic, and clinical data from electronic medical records (clinical history of asthma and atopy, family history of atopic diseases, atopy defined by elevated total IgE or specific IgE >0.35 kUA/L to at least one of standard panel of common inhalant allergens).

Thirty-five patients (35.4%) were prescribed ICS, at a median equivalent daily dose of 500 [interquartile range, IQR, 400-800] microgram of beclomethasone. 24/35 were on fixed-dose combinations with long-acting beta agonists (LABA). Only 3 patients in the ICS group and 1 in the non-ICS group had asthma listed as a diagnosis. In 10/35 patients, ICS had been started for

recurrent wheeze as per clinic letters, no information as to the indication for ICS was available for the remaining 25 patients. Five patients had a family history of asthma, all of whom were in the ICS-group. Patients prescribed ICS were significantly older and had been older at diagnosis (Table 1). Caucasian ethnicity was associated with an increased odds ratio (OR) of being prescribed ICS (OR 2.4, 95% confidence interval, 95% CI, 1.03-5.7). No ultrastructural defect was more frequent in the ICS-group. 49/96 (51%) were atopic with no significant difference in prevalence of atopy between the ICS and non-ICS group. Groups did not differ significantly in nasal NO, blood eosinophils, total IgE (kUA/L or z-scores), serum Vitamin D – a parameter that has been associated with lung health, particularly in asthma - , or forced-expiratory volume in one second (FEV_1) %predicted (ALPHA™ Touch Fleisch Pneumotachograph, Vitalograph, Buckingham, UK, Rosenthal reference equations [5]). We confirmed that reversible airway obstruction is common in PCD [6] (BDR >12%, the National Institute for Health and Care Excellence (NICE) guidelines (https://www.nice.org.uk.), with 16 patients (27%) having BDR >12% but there were no distinguishing features in those with BDR. BDR was not associated with atopy (OR 2.13, 95% CI 0.5-8.5), raised FeNO (OR 0.9, 95% CI 0.1-7.7) or being prescribed ICS (OR 2.1 95% CI 0.54-8.2). FeNO, a marker of airway eosinophilia, was generally low, as described previously [7], with no significant difference between the groups. 35 patients underwent bronchoalveolar lavage, 17 of whom had been prescribed ICS at the time of bronchoscopy. Neutrophilia was the most common finding, but BAL eosinophilia was reported in only 1 patient on ICS and 2 patients not on ICS. There was no difference between groups in lung clearance index (LCI, multiple breath inert gas washout measurements with sulphur hexafluoride) or the prevalence of bronchiectasis on HRCT, both of which are markers of disease severity.

We found that ICS are commonly prescribed in PCD often without evidence of Type 2 airway inflammation. There was a high frequency of atopy and reversible bronchial obstruction, which

may have suggested Type 2 airway inflammation would be common. However, reversible airflow obstruction may be due to mucus shifting, and indeed the greater bronchodilatation previously reported with exercise rather than short acting β-2 agonist supports this view [6]. Objective evidence of Type 2 inflammation was scarce: only 4 patients had positive BDR with evidence of eosinophilia (blood and/or airways), and 3 patients were atopic, had BDR and evidence of eosinophilia (data available for n=57). Airway eosinophilia, a hallmark of Type 2 airway inflammation and response to ICS [8], was rare. Patients on ICS were significantly older, and in 20/35 patients ICS treatment was started prior to being diagnosed with PCD, implying that they had been incorrectly treated as asthma. However, the decision to continue the prescription of ICS may be irrational.

Although ICS are safe, high doses such as were prescribed to many PCD children carry an increased risk of systemic side effects, including adrenal suppression and growth retardation [9]. ICS may also cause topical immunosuppression, which could impair airway immune responses [10]. More recently, ICS have been linked with non-tuberculous mycobacteria (NTM) lung disease in chronic respiratory diseases [11]. No cases of NTM lung disease were identified in our cohort.

This is the first study assessing ICS prescription in PCD based on individual patient data, and the strength of our study is its size, nearly a quarter of all children with a known diagnosis of PCD in England. We highlight that ICS are prescribed more frequently in Britain than previously estimated in questionnaire based European study [12]. The main weakness is the lack of induced or spontaneously expectorated sputum to classify airway inflammation. We did not measure airway reactivity, as recommended in the American PCD treatment guidelines, but many patients had airflow limitation precluding bronchial challenge testing [13]: 22 out of 83 patients had FEV_1 <70% (27%), 10 of whom had FEV_1 < 60% (12%). In addition, as with BDR, bronchial hyper-responsiveness is not specific for Type 2 inflammation [14]. We also

acknowledge that we do not have data on adherence to ICS, or pre-ICS data on airway inflammation and bronchodilator responsiveness, and we have pooled patients on ICS and combined ICS + LABA, potentially leading to false negative BDR due to LABA action. However, this does not detract from our conclusions, because ICS should be used to target Type 2 inflammation, not BDR which is non-specific. It could be argued that some patients prescribed ICS had had a treatment response, and the ongoing prescription was rational. However, without a formal double blind, placebo controlled therapeutic trial, placebo effects cannot be excluded, and there is no scientific basis for a beneficial effect of ICS on neutrophilic airway inflammation. Our findings resemble previous practice in cystic fibrosis (CF), where ICS were widely used as anti-inflammatory drugs in an attempt to treat recurrent wheeze but are no longer recommended due to lack of evidence of beneficial effects [15]. In PCD, randomised controlled ICS trials are needed to clarify if they have any role outside treatment of Type 2 inflammation.

In summary, ICS are not being used rationally in PCD and ICS prescription is inappropriate in PCD unless there is evidence of Type 2 airway inflammation.

Table 1. Characteristics of patients treated with ICS versus not treated with ICS.

Patients' characteristics	**ICS**	**No ICS**	**p-value**
n (m/f)	35 (13/22)	64 (34/30)	0.15†
Age (years, median [IQR])	13 [7.8-15]	9.8 [4.9-13]	<0.05§
Age at diagnosis (years, median [IQR])	7.4 [3.3-11.2]	2.6 [0.3-6.9]	<0.05§
Ethnicity n (%)			
Caucasian	20 (57%)	23 (36%)	0.05†
South-East Asian	7 (20%)	29 (45%)	
Other*	7 (20%)	10 (16%)	
Missing data	1 (3%)	2 (3%)	
Nasal NO (pbb) (n=56)	**median [IQR]**		
	75 [48-94]	63 [37-112]	1.00§
Ciliary ultrastructure defect n (%)			
Outer dynein arm defect (ODA)	13 (37%)	30 (47%)	
Inner dynein arm defect (IDA)	0	3 (5%)	
ODA+ IDA	6 (17%)	10 (15%)	
IDA with microtubule disorganization	7 (20%)	5 (8%)	0.10†
IDA + radial spoke defect	1 (3%)	0	
Transposition	1 (3%)	3 (5%)	
Normal	7 (20%)	13 (20%)	
Atopy (n=96)			
n	21 (60%)	28 (44%)	0.21†
Total IgE (kUA/L)	86 [17-262]	25 [13-130]	0.18§
Blood eosinophils (10^9/L) (n=95)	**median [IQR]**		
	0.2 [0.2-0.4]	0.2 [0.1-0.4]	0.53§
FeNO (pbb) (n=44)	**median [IQR]**		
	7 [5-10.5]	8 [5.3-13]	0.31§
Serum Vitamin D			
nmol/L	47 [32-57]	55 [35-69]	0.25§
< 50 nmol /L (n)	13/23 (57%)	23/52 (41%)	0.33†
Spirometry	**median [IQR]**		
FEV_1 % predicted	82 [68-88]	81 [69-91]	0.64§
Reversible airway obstruction			
% change FEV_1	7 [2-15]	5.5 [1.5-12]	0.43§
BDR >12% (n (%)	7/22 (32%)	9/37 (24 %)	0.56†
Bronchoalveolar lavage (n=35)			
Eosinophilia	1	2	
Neutrophilia	11	11	
Lymphocytosis	2	1	
Normal Diff.	1	1	
Diff. not done	2	3	
Lung clearance index	**median [IQR]**		
LCI score	9.6 [8.4-10.9]	7.9 [7.2-8.7]	0.06§
Chest CT			
Normal (n)	3	7	0.73†
Bronchiectasis (n)	18	30	

m – male; f – female; IQR – interquartile range; *African, Turkish, mixed; pbb – parts per billion; BDR – bronchodilator reversibility; CT – computed tomography. † Fisher's exact test, § Mann-

Whitney-U test. Non-Caucasian groups were pooled for statistical analysis; IDA defects with microtubule disorganization have been associated with a more severe clinical course and were compared to all other ultrastructural defects. In the 20 patients whose cilia were normal in transmission electron microscopy PCD was diagnosed based on genetics and clinical phenotype.

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