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Title

One year outcomes in a multi-centre cohort study of incident rare diffuse parenchymal lung disease in children (ChILD)

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Dr Cunningham reports other from Boehringer Ingelheim, outside the submitted work; Dr Griese reports other from Vertex and Boehringer Ingelheim, outside the submitted work; Dr. Schwerk reports other from Boehringer Ingelheim, outside the submitted work; Drs. Graham, MacLean, Aurora, Ashworth, Barbato, Calder, Carlens, Clement, Hengst, Kammer, Kiper, Krenke, Kronfeld, Lange, Ley-Zaporozhan, Nicholson, Rue, Wesselek, Wetzke, Bush, have nothing to disclose.

ABSTRACT

We performed a prospective, observational, cohort study of children newly diagnosed with Children's interstitial lung disease (chILD), with structured follow up at 4, 8, 12 weeks, and 6 and 12 months. 127 children, median age 0.9 (iqr 0.3, 7.9) years had dyspnoea (68%, 69/102), tachypnoea (75%, 77/103) and low oxygen saturation (SpO_2) median 92% (iqr 88, 96). Death (N=20, 16%) was commoner in those <6 months of age with SpO_2 <94% and developmental/surfactant disorders. We report for the first time that chILD survivors improved multiple clinical parameters within 8-12 weeks of diagnosis. These data can inform family discussions and support clinical trial measurements.

INTRODUCTION

Interstitial lung disease in children (ChILD) encompasses more than 200 entities[1], many so rare that there is no reported prospective longitudinal disease phenotyping[2]. Recent improvements in adult interstitial lung disease phenotyping has led to better disease management. We aimed to utilise the first international collaboration for chILD to systematically study new diagnoses for 12 months, to better understand disease progression and support the development of clinical outcomes.

METHODS

This was an observational cohort study of children (<18 years) presenting to participating hospitals with a new clinical presentation of chILD, submitted to the chILD-EU Registry (www.childeu.net) between December 2013 and March 2016[3]. Cases were registered following brief screening questions and were subject to multidisciplinary peer review to standardise diagnostic precision[3]. Common causes of diffuse lung disease (i.e. cystic fibrosis, respiratory distress syndrome) were excluded. There were 133 incident cases during this period. Six were excluded from analysis, leaving 127 reported here (1 time from diagnosis too great, 2 airway disease, 1 pleural disease, 2 insufficient data). The enrolment date (baseline data) was the study start date. Study variables were collected at baseline, 4, 8, 12 weeks, and 6 and 12 months (end of the study), and included patient demographics, initial diagnoses, family and neonatal history, current history and symptoms, physical examination findings, Fan score[4], laboratory results and treatments trialed and current (see study protocol (https://www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/ukcrc-studies/child-eu) and ChILDEU website (www.childeu.net) for study variables and standardisation standard operating procedures)[5,6]. Biobank materials included (where

available) chest radiology (CT), genetic mutation analysis and lung biopsy. Investigation and treatment recommendations were standardised[7]. Ethical and legal approvals and were present in all recruiting centres. Fully informed parental consent was obtained prior to study inclusion.

Comparison of continuous variable was by Mann-Whitney test (where only two categories i.e. dead/alive) or Kruskal-Wallis test (> two categories i.e. baseline oxygen levels). Missing SpO_2 values were imputed (see supp methods). Height, weight and BMI were converted to Centre for Disease Control z-scores and percentiles[8]. FEV_1 and FVC were converted into Global Lung Initiative z-scores and percentiles[9]. The trial is registered on clinical trials (https://clinicaltrials.gov/ct2/show/NCT02852928)

RESULTS

Participants were from nine European countries, predominantly Germany, UK and Poland (Supp. Table 1). The proportion of participants providing follow up data (or dead) at each time point ranged from 76-83% (Supp. Table 2). Median age at baseline was 0.9 (iqr 0.3, 7.9) years (Supp. Table 1). Peer review diagnosis, investigations and treatments are provided in supplementary information (Supp. Table 3, 4 and 5). At baseline, dyspnoea (68%, 69/102) and tachypnoea (75%, 77/103) were frequent, with failure to thrive in 49% (61/125) common (Supp. Table 6). Baseline SpO_2 in room air ≤94% was recorded in 53% (65/122) at a median 92% (iqr 88, 96). Lower baseline SpO_2 was most common in younger infants related to growth, developmental or surfactant related disorders (Supp. Table 3, Fig 1).

There were 20 deaths (16%) over 12 months. Age at death, time from enrolment to death and diagnostic group are provided in Supplementary Table 3. Most deaths occurred in diffuse developmental disorders (N=6), alveolar surfactant disorders (N=6) and lung growth abnormalities (N=3). Age at baseline was significantly associated with survival, with deaths in 33% (15/45) of those < 6 months of age compared with 7% (5/74) in those ≥6 months of age (log-rank statistic, p=0.0001), Fig 1a. SpO_2 at baseline ≥94% was associated with better survival (4% died: 2/52), compared with 29% (18/63) of those with SpO_2 <94%, (p=0.0006), Fig 1b.

Over 12 months, ventilatory support was utilised in 49 (39%) children, decreasing steeply over time with improvement or death (Table 1). Of the 31 children ventilated at baseline, 15 died (11 invasive, four non-invasive ventilation). Supplemental oxygen was provided to 72% (92/127) at any point from baseline to 12 months. The percentage of children in follow up recorded as receiving oxygen supplementation declined most markedly from baseline (63%, 74/117) to 12 week observations (31%, 23/74). For 33 children (26%), SpO_2 in air was never ≥94%, mostly in those who subsequently died or were aged <6 months of age at baseline (Table 1). Most improvement in SpO_2 in air was observed in the first 8 weeks following enrolment (Supp Figs 1a/b and 3).

There was a progressive reduction over time in Fan scores (Figure 2 and Supp Fig 1c), predominantly in the first 12 weeks, but continuing up to 12-months (Supp. Fig 4), with deaths more frequent at higher baseline scores (5 (36%, 8/22) and 4 (23%, 9/40)).

Weight for age at baseline was low and remained so at 12 months (Supp. Table 7). Most improvements in weight and height occurred in the first 4 weeks, with slower gains thereafter. Lower weight and height z-score at baseline was significantly associated with lower baseline SpO_2 and death (Supp. Fig. 5).

Median respiratory rate tended to be higher than age related reference values[10] at baseline but similar to age adjusted reference values by 12 months. Median heart rate was similar to age related reference values across observations[10], Supp. Figure 6 (a-d).

Improvement in FEV_1 % predicted and z score continued up to 12 weeks, with little subsequent change (Table 1). FVC had a more progressive change over the 12-month observation period, again most marked in the first 12 weeks (FVC % predicted median 48% to 65%, and to 80% by 12 months). At baseline 19/25 (76%) spirometry demonstrated a restrictive (FEV1/FVC ≥0.8) and 6/25 (24%) an obstructive pattern (ratio <0.8).

Systemic corticosteroids were provided to 58% (73/125), hydroxychloroquine 28% (35/126), and azithromycin 36% (45/126) of cases over the observation period (supplementary information).

DISCUSSION

We report that many clinical parameters appeared to improve within 8-12 weeks of diagnosis and starting treatment in children with chILD. To our knowledge this is the first prospective, longitudinal, cohort assessment of chILD. At 12 weeks when compared with baseline, provision of oxygen supplementation was observed in 31% fewer children, and lung function was 29% greater for FVC and 24% for FEV_1. Mean Fan scores were 29% lower at 12 weeks. Differences in respiratory rate (and heart rate) across timepoints when related to normative data were not observed to have notable differences. We did not however provide a formal longitudinal analysis and this together with missing data may have impacted the results. We also acknowledge potential bias may have occurred from the effect of funding limitations on recruitment in some EU countries and translation of study materials. In summary, we have identified key parameters responsive to change in chILD

which could be used in trials of treatment and inform prognostic discussions with families. Furthermore, we suggest that chILD patients should be seen more frequently in the first 3 months following diagnosis so treatment can be adjusted with any clinical improvement.

Table 1
Deaths, clinical support and physiology by study visit

	Deaths	Non Invasive Ventilation		Invasive Ventilation		Supplemental Oxygen		SpO2 ≥94% in air		Spirometry	FVC (% predicted)	FEV1 (% predicted)
		N	%	N	%	N	%	N	%	N	Median (iqr)	Median (iqr)
Prior to baseline	0	41/126	33	43/126	34	93/125	74	-	-	-	-	-
At baseline	0	18/114	16	16/116	14	74/117	63	57/122	47	25/36	48 (34,73)	50 (35, 68)
4 weeks	10	6/80	8	6/80	8	37/80	46	47/83	57	17/36	59 (44, 79)	66 (49, 76)
8 weeks	15	2/76	3	3/75	4	29/75	39	52/78	67	17/36	65 (46, 83)	67 (46, 81)
12 weeks	16	3/74	4	2/72	3	23/74	31	54/74	73	18/36	77 (57, 86)	74 (56, 85)
6 months	20	4/84	5	2/83	3	27/83	33	62/82	76	21/36	75 (61, 84)	70 (59, 78)
12 months	20	2/72	3	1 /71	1	16/69	23	54/70	77	18/36	80 (69, 96)	74 (65, 89)

Figure Legends

Figure 1
Survival by Kaplan Meier for (a) age < or ≥ 6 months (b) baseline room air SpO_2 < or ≥ 94%.

Figure 2
Change of Fan score over observation period (numbers in bars represent number in each group)

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