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The improved clinical course of persistent tachypnea of infancy with inhaled bronchodilators and corticosteroids

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Abstract

Background: Persistent tachypnea of infancy (PTI) is the most common interstitial lung disease in young children. As no standardized therapeutic guidelines exist, different pharmaceuticals are used to treat PTI; inhaled corticosteroids (ICS) and bronchodilators being mostly used. This observation assessed the effectiveness of bronchodilators and ICS in children with PTI enrolled in the children's interstitial lung diseases (chILD)-EU Register.

Methods: Symptomatic children with PTI were observed according to a predetermined stepwise protocol including bronchodilators as the first choice treatment (6 weeks). In patients with incomplete response, additionally, ICS was given (12 weeks). Signs, symptoms, and pulmonary function were evaluated at three time points: at baseline, 6 (±1) weeks after initiation of bronchodilators, and 12 (±1) weeks after bronchodilators/ICS.

Results: Thirty-one children (median age: 44 months, interquartile range [IQR]: 15–67) were included. The therapy was associated with a significant reduction of tachypnea (53.3% of patients, $p = 0.02$), exercise intolerance (52.2% of patients, $p < 0.001$), chest retractions (43.8% of patients, $p = 0.04$), and crackles (29.2% of patients, $p = 0.02$). Also, a significant improvement in forced expiratory volume in 1 s (FEV_1) (median z score: −2.21 vs. −0.47, $p = 0.03$), residual volume (RV) (median z score 5.28 vs. 1.07, $p = 0.007$), RV% total lung capacity (TLC) (median z score: 6.05 vs. 1.48, $p = 0.01$), sRaw (median z score: 6.6 vs. 4.64, $p = 0.01$), R5 (median z score: 1.27 vs. 0.31, $p = 0.009$), and R5–R20 (median: 0.58 vs. 0.26 kPa/(l/s), $p = 0.002$) was demonstrated.

Conclusions: Inhaled bronchodilators and ICS may exert a positive effect on the severity of symptoms and pulmonary function test (PFT) in symptomatic children with PTI. However, a randomized control trial should be conducted to confirm their effectiveness.

KEYWORDS

children interstitial lung disease, inhaled treatment, neuroendocrine cell hyperplasia of infancy, pulmonary function tests

1 | INTRODUCTION

Children's interstitial lung diseases (chILD) encompass a heterogeneous group of rare and diverse disorders associated with substantial morbidity and mortality.[1] Recent classification identified a subgroup of diseases more prevalent in children less than 2 years old, which includes, among others, persistent tachypnea of infancy (PTI).[2,3] After excluding other conditions of this age group, high-resolution computed tomography (HR-CT) is highly sensitive for the diagnosis of PTI.[4,5] A lung biopsy is only necessary when there are contradictory findings.[1,2,4,6–8] If performed, tissue usually shows increased neuroendocrine cells, warranting the label neuroendocrine hyperplasia of infancy (NEHI).[9]

PTI insidiously starts during the first year of life, and the most common clinical features include tachypnea, chest retractions, crackles, hypoxemia, and failure to thrive.[10–13] HR-CT typically reveals sharply defined ground-glass opacities (GGO) localized in the middle lobe, the lingula, and the paramediastinal and perihilar regions, as well as air trapping.[5,14]

The clinical course of PTI is mostly mild or moderate, and affected children gradually improve during childhood.[15] However, some patients require oxygen supplementation for a longer time[11,16] and sometimes symptoms may persist until adulthood.[16,17]

Data on pulmonary function tests (PFTs) in children with PTI are sparse.[18] The most common abnormalities found are peripheral airway obstruction and hyperinflation.[12,16,19,20] Bronchial obstruction reversibility testing is usually negative.[12,19] In the majority of children, lung function normalizes by school age.[15] However, some authors report the persistence of the abnormalities into late childhood.[17]

No therapy guidelines are available, and treatment is mainly based on expert opinion indicating that children with PTI should receive symptomatic and preventive care. Oxygen supplementation, nutritional support, or artificial feeding are indicated when needed. Moreover, treatment of comorbidities, that is, gastroesophageal reflux, and interventions to prevent infections are recommended.[1,21] A causative treatment of PTI is unknown. Various therapies have been tried. Affected infants were treated with systemic corticosteroids, inhaled corticosteroids (ICS), and inhaled bronchodilators. There are also reports of oral azathioprine and hydroxychloroquine usage.[10–13,20,21] To date, it has not been demonstrated that any therapeutic intervention has contributed to the cessation or significant reduction of the severity of symptoms in children with PTI. However, it should be considered that these data were derived from retrospective analyses of single cases, case series, and unsystematic observations only.

Resulting from those inconclusive data, chronically affected children are often treated with inhaled bronchodilators or ICS in a very individual way. In the frame of the chILD-EU registry, the collaborators agreed upon a structured approach to applying the inhaled treatment. It was the decision of the attending physician to follow the proposed scheme. Treatment episodes were systematically collected and prospectively analyzed to assess the impact of bronchodilators and ICS on the clinical symptoms and PFT results in children with PTI.

2 | METHODS

2.1 | Patients

The child-EU Register is a web-based platform that prospectively collects data of rare pediatric lung disorders focusing on chILD (www.childeu.net).[22] For this analysis, symptomatic patients with PTI whose attending physicians decided to follow the predetermined treatment regimen, as described below, were eligible.

Diagnosis of PTI was based on the presence of chronic clinical symptoms, including tachypnea, intercostal retractions, crackles, hypoxemia, and the characteristic HR-CT findings with GGO in the right middle lobe, lingula, perihilar and pericardial region. In case of ambiguous HR-CT findings, a lung biopsy was performed.

Patients were recognized as symptomatic if at least two of the following abnormalities were present at the baseline visit: tachypnea defined as respiratory rate ≥ 90 percentile of normal range,[23] dyspnoea with chest retractions, crackles on auscultation, exercise intolerance reported by a caregiver, and/or a child, hypoxemia <92% SpO_2 in room air, failure to thrive (body mass index [BMI] ≤ 5 percentile according to WHO centile charts)[24] and abnormalities on PFT. Airway obstruction was defined as a reduction in the ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC)—z score < −1.645; air trapping was defined as increased residual volume (RV) to total lung capacity (TLC) ratio—z score > 1.645. Increased specific airway resistance (sRaw), increased respiratory resistance to 5 Hz (R5), and increased respiratory resistance to 20 Hz (R20) was defined as z score >1.645. Decreased reactance to 5 Hz (X5) and decreased resonant frequency (Fres) were defined as z score < −1.645.[25] Lung clearance index (LCI) ≥ 7 was considered abnormal.[26]

Not included were children with (1) lower respiratory tract infections within 4 weeks before baseline visit, (2) treatment with bronchodilators (short-acting β 2-agonists, long-acting β 2-agonists, cholinolytics), or ICS within the last 8 weeks.

2.2 | PFTs

Spirometry, body plethysmography, impulse oscillometry, and multiple breath washout tests were performed in cooperating children. Spirometry and body plethysmography were performed according to the European Respiratory Society (ERS) American Thoracic Society (ATS) consensus.[27,28] Reference equations from the Global Lung Function Initiative (GLI) were used to calculate z scores.[29] The impulse oscillometry included the measurements of R5, R20, X5, Fres, and reactance area (AX). For data analysis, the Dencker et al. reference values were used.[25] Spirometry and impulse oscillometry were performed with Jaeger® Vyntus IOS (Care Fusion) equipment and body plethysmography with a Masterscreen Body device. Multiple breath washout assessment was conducted with Exhylazer D® and Spiroware® version 3.2. Eco Medics AG. The mean of at least two technically acceptable quality measurements was calculated. LCI, S_{acin}, and S_{cond} were assessed.

2.3 | Treatment applied and clinical response assessment

At baseline, children who met the criteria mentioned above-received bronchodilators. The choice and dose of the drug were age-dependent (Table 1). After 6 (±1) weeks, the evaluation of treatment outcomes was performed by the physician treating the patient. Children who achieved improvement continued bronchodilators as the only intervention. In the case of persistence of any symptom, ICS were added. The next visit was scheduled after another 12 (±1) weeks to assess the treatment effect achieved during the observation period (Figure 1).

Clinical improvement was defined as the resolution of retractions, tachypnea, or auscultatory abnormalities, $SpO_2 > 92\%$, weight gain–BMI > 5 percentile, and exercise tolerance improvement. The minimal clinically important difference (MCID) in PFTs was defined as: increase in FEV_1 and FVC ≥ 10%,[30,31] decrease in R5 ≥ 30%[32]; increase in X5 ≥ 36%,[33] decrease in sRaw ≥ 20%,[34] decrease in AX ≥ 29%,[35] decrease in RV/TLC ratio ≥ 11%,[36] decrease in RV ≥ 12%,[36] and decrease in LCI > 1.[37] Adverse events were recorded by patients or caregivers and reviewed at each visit.

2.4 | Statistical analysis

Data were analyzed using Statistica 13 software package (StatSoft, Inc.). The results are presented as medians and interquartile ranges (IQR). The significance of differences in the values of quantitative parameters at three time points was evaluated using the analysis of variance (ANOVA) test for repeated measures (for variables with normal distribution) and the Friedman test (for nonnormal distribution). The post hoc analysis was performed to study multiple pairwise comparisons. The Cochran's *Q* test was used to assess the significance of the difference in the values of categorical variables with two levels in consecutive measurements. $p < 0.05$ was considered statistically significant.

2.5 | Ethics statement

All the caregivers and the patients aged ≥ 16 years old provided written informed consent and verbal permission to participate in the Kids Lung Register. The Ethics Commission approved the registry–the Ludwig Maximilians University of Munich (EK 026-06, 257-10, 111-13, 20-329) and the Medical University of Warsaw (AKBE/151/2018). Before the analysis was conducted, written informed consent was provided by the parents or guardians of patients.

3 | RESULTS

Thirty-one children with a median age of 44 months (IQR: 15–67; range: 7–157) were enrolled in the study. Children under 5 years of age ($n = 22$) constituted more than 70% of all patients (12 children < 2 years; 10 children between 2 and 5 years) (Table S1). At baseline, after 6 weeks and after another 12 weeks, the number of children evaluated was 31, 31, and 27, respectively (parents of four children refused to come for a final evaluation due to various reasons not related to medical conditions). As an incomplete resolution of symptoms was found at the second visit in all children, all of them were further scheduled for combined therapy with bronchodilators and ICS.

In 26 (83.9%) patients, PTI was diagnosed based on clinical presentation and HR-CT images. Due to ambiguous HR-CT findings, lung biopsy contributed to the diagnosis in the remaining five children (16.1%). All lung biopsy specimens had increased neuroendocrine cells and no other abnormalities and were consistent with NEHI. The median age at PTI diagnosis was 10 months (IQR: 6.5–15; range: 0–44). Hence, the median time between the PTI diagnosis and study onset was 26 months (IQR: 3.5–53.5; range: 0–145).

3.1 | Clinical symptoms

Crackles (77.4%), exercise intolerance (74.2%), and hypoxemia (58.1%) were the most common PTI signs and symptoms reported at baseline. The highest prevalence of signs and symptoms was found in children younger than 5 years of age. Older children were less symptomatic. In the two oldest teenagers, only crackles on auscultation were found (Table S1). The applied treatment was associated with the improvement of clinical symptoms (Table 2, Figure 2). At the final evaluation, the number of children with tachypnea, exercise intolerance, chest retraction, and crackles significantly decreased in 53.3%, 52.2%, 43.8%, and 29.2% of cases, respectively (Table 2). It should be emphasized that the number of patients with crackles and

TABLE 1 Age-dependent selection of treatments and doses used

Age (years)	Therapeutic intervention one	Therapeutic intervention two
0–4	Fenoterol 50 μg plus ipratropium bromide 20 μg tds (MDI with spacer)	Therapeutic intervention one plus: Fluticasone propionate 100 μg bid (MDI with spacer)
4–12	Salmeterol 50 μg bid (MDI with spacer)	Therapeutic intervention one plus: Fluticasone propionate 250 μg bid (MDI with spacer)
>12	Salmeterol 100 μg bid (MDI with spacer)	Therapeutic intervention one plus: Fluticasone propionate 500 μg bid (MDI with spacer)

Abbreviations: bid, two times a day; MDI, meter dose inhalator; tds, three times a day.

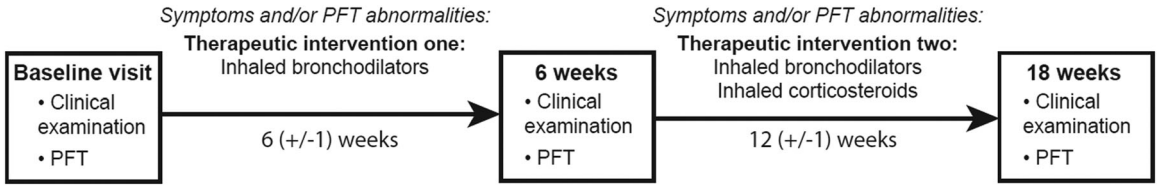

FIGURE 1 Study of the structured observation. PFT, pulmonary function test

TABLE 2 The number and percentage of patients with specific signs and symptoms over time

Parameter	Baseline visit ($n = 31$)	6 weeks ($n = 31$)	18 weeks ($n = 27$)	p
Failure to thrive, *n* (%)	5 (16.1)	2 (6.5)	2 (7.4)	0.11[a]
Tachypnea, *n* (%)	15 (48.4)[0-2]	12 (38.7)	7 (25.9)[0-2]	**0.02**[a]
Respiratory rate, median (IQR)	30 (20–65)[0-2]	28 (20–50)	28 (20–50)[0-2]	**0.008**[b]
Chest retractions, *n* (%)	16 (51.6)	13 (41.9)	9 (33.3)	**0.04**[a]
Crackles, *n* (%)	24 (77.4)[0-1]	17 (54.8)[0-1]	17 (63)	**0.02**[a]
Hypoxemia, *n* (%)	18 (58.1)	15 (48.4)	11 (40.7)	0.17[a]
Exercise intolerance, *n* (%)	23 (74.2)[0-1, 0-2]	11 (35.5)[0-1]	11 (40.7)[0-2]	**<0.001**[a]

Note: Statistically significant values (<0.05) are shown in bold.

Abbreviations: IQR, interquartile range; n, number.

[a]Cochran's *Q* test.

[b]Friedman test.

[0-1]Significant difference between evaluation at baseline and evaluation after therapeutic intervention one ($p < 0.05$ post hoc test).

[0-2]Significant difference between evaluation at baseline and evaluation after therapeutic intervention two ($p < 0.05$ post hoc test).

exercise intolerance decreased significantly after 6 weeks of treatment with bronchodilators only. Moreover, after 18 weeks of treatment, in 11 children, a reduction of auscultatory signs was observed, and 10 patients declared an improvement in exercise tolerance.

3.2 | PFTs

At baseline, acceptable spirometry maneuvers were obtained in 11 patients. The obstructive ventilatory defect was found in three patients (23.7%) while decreased FEV_1 and FVC in six (54.5%) and five (45.5%) patients, respectively. There was a significant increase in FEV_1 and FVC values and FEV_1 *z* scores between baseline and the final assessment (Table 3, Figure 3). According to MCID defined above, the improvement in spirometry measurements was achieved in 8 out of 11 patients in FEV_1 and FVC values.

All six patients, who were able to perform body plethysmography at the time of enrolment had elevated sRaw. In the majority of them, RV% TLC was above the upper limit of normal (83.3%). After the therapy, values of sRaw, RV% TLC, and RV significantly decreased in the study group (Table 3, Figure 3). Improvement was significantly related to the use of bronchodilators. The addition of ICS did not result in further improvement of the analyzed parameters. The percentage of patients who achieved MCID in sRaw, RV% TLC, and RV were 66.7%, 66.7%, and 83.3% respectively.

Eleven children performed impulse oscillometry maneuvers at baseline. Peripheral resistance (R5–R20) significantly decreased between baseline and the third visit (Table 3, Figure 3). Abnormally high airway resistance at 5 Hz was observed in five (45.5%) children, and in all of them, it decreased to the normal range after treatment. There was a significant improvement of R5 and AX values between the baseline and both subsequent visits. The MCID criteria for baseline and posttreatment values of R5, AX, and X5 were fulfilled in 18.2%, 54.5%, and 36.4%, respectively. Most of the parameters measured in impulse oscillometry improved after treatment with bronchodilators. The only exception was R5–R20—a parameter reflecting the status of the peripheral airways. A significant reduction in R5–R20 was observed only after the completion of 18-week treatment with both bronchodilators and ICS.

LCI value was elevated over seven in all children at the time of enrolment (median: 9.91; IQR: 9.5–13.72) and remained abnormal throughout all follow-up visits. Nonetheless, treatment with bronchodilators resulted in a decrease of LCI > 1 in two patients.

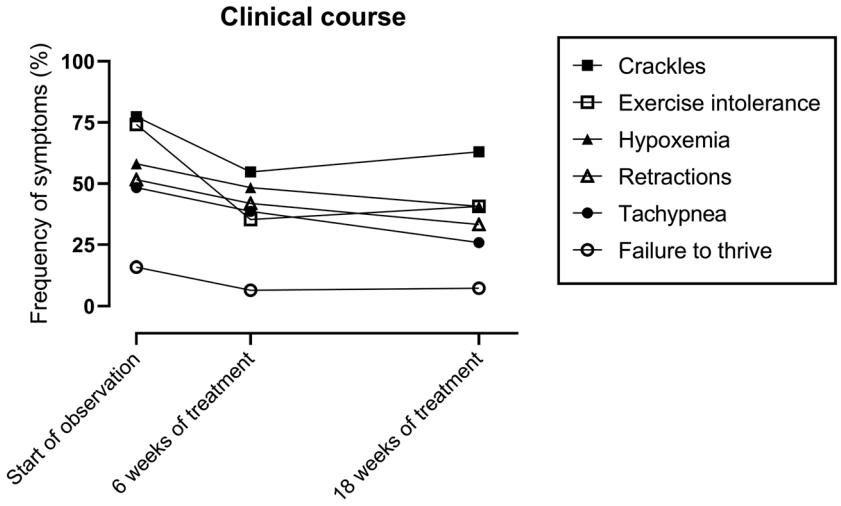

FIGURE 2 Improvement of clinical signs and symptoms over time

4 | DISCUSSION

This is the first prospective observation in a decent group of symptomatic children with PTI, evaluating treatment effects of inhaled bronchodilators and corticosteroids on the clinical course and pulmonary function. We demonstrated a potential benefit from the use of the inhaled drugs in this group of subjects. Treatment resulted in a significant decrease in symptoms severity, including tachypnea, retractions, crackles, and exercise intolerance. Consistent improvement was also found for various PFT parameters, particularly for those reflecting the peripheral airways' function.

Data on treatment efficiency in children with PTI are scarce, and only case reports, small series, and occasional retrospective analyses of small groups exist.[10–12,20] As PTI is a chronic disorder, various medications to reduce symptoms severity are used. A survey study of 40 NEHI patients reported a wide range of drugs recommended by physicians: 60% of children were treated with inhaled bronchodilators, 38% with ICS, 34% with systemic corticosteroids, and 31% with antireflux medications.[21] A recent study confirmed that almost 20% of PTI children at school age used ICS.[15] However, to date, no high-quality studies to assess the effectiveness of any kind of treatment in children with PTI have been conducted.

The common use of bronchodilators in the treatment of PTI is mainly based on the pathophysiology of the disease, which leads to small airway obstruction. Bearing in mind a beneficial effect of this class of drug in other conditions associated with airflow limitation, the rationale for PTI treatment with bronchodilators seems reasonable when no other effective therapies have been developed. An additional argument for the use of bronchodilators is that in NEHI, which is the most common form of PTI, the main histopathological finding is an increased number of neuroendocrine cells. These cells secrete vasoactive and bronchoactive mediators, for example, serotonin that can induce bronchospasm.[39] Therefore, an attempt to counteract their bronchoconstrictive effect may be justified. As mentioned above, steroids are also commonly used to treat PTI, albeit such therapy is questionable from a pathophysiological point of view. Corticosteroids are known to be the most effective in eosinophilic inflammation,[40] which is not the case in children with PTI.[11] The frequent practice of combined PTI treatment with bronchodilators and ICS probably derives from experience in the treatment of asthma.

Our observation suggested that inhaled treatment could be beneficial for children with PTI. The lack of the control group did not allow to definitively differentiate whether the improvement was associated with the intervention or was a consequence of the natural course of the disease. Previous studies suggest that tachypnea resolution occurred around the age of 2.4–3.7 years, and hypoxemia persisted up to the age of 3.6–9.0 years.[4,11,15,16] The exercise tolerance impairment seems to be the longest-lasting symptom in the natural course of the PTI. It can persist even up to adolescence.[11,16] In our cohort under treatment resolution of symptoms was faster than indicated above. Tachypnea resolved in over 50% of children within 18 weeks. More than half of the parents or children reported an improvement in exercise tolerance. The caregivers noticed less effort while eating and playing in younger children, and older patients reported less fatigue during physical activities. Also, 7 out of 18 children were no longer oxygen-dependent within this short period.

Our investigation also indicated a significant improvement in lung function. Both commonly measured spirometry parameters and those reflecting the peripheral airways' function improved (FVC, FEV_1, sRaw, RV, RV% TLC, R5, R5–R20, AX). A substantial decrease in lung hyperinflation (the median decline in the RV was almost 1 L) and a reduced respiratory resistance was observed.

It is worth noting, that at baseline, FEV_1 and FVC were abnormal in more than 50% of cases, while less than a quarter of children met a spirometry criterion for airway obstruction. This can be explained by the fact that the FEV_1/FVC ratio represents the functional status of large and medium-sized bronchi. Albeit in children with PTI, abnormalities in the peripheral airways are expected primarily.[9] The posttreatment improvement in FEV_1 and FVC without significant effect on FEV_1/FVC ratio is consistent with a substantial improvement of small airways obstruction. The

TABLE 3 Spirometry, body plethysmography, and impulse oscillometry results

Spirometry parameter, unit	Baseline visit (*n* = 11) Median (IQR)	6 weeks (*n* = 11)	18 weeks (*n* = 11)	*p*
FEV_1, *z* score	−2.21 (−2.51 to −0.74)$^{0-2}$	−1.65 (−1.96–0.37)	−0.47 (−1.71 to −0.11) $^{0-2}$	**0.03**[a]
FEV_1, l/s	1.07 (0.94–1.63)$^{0-2}$	1.38 (1.14–1.43)	1.37 (1.16–1.52) $^{0-2}$	**0.003**[a]
FVC, *z* score	−1.46 (−2.33 to −0.03)	−0.52 (−2.02– 0.51)	−0.17 (−0.93 to −0.01)	0.15[b]
FVC, l	1.24 (1.0–1.86)$^{0-2}$	1.45 (1.22–1.85)	1.57 (1.32–1.76) $^{0-2}$	**0.02**[a]
FEV_1% FVC, *z* score	−0.34 (−2.25–0.72)	−1.11 (−1.63 to −0.25)	−0.44 (−1.47 to −0.05)	0.9[a]
FEV_1% FVC, %	90.33 (75.8–94.38)	88.18 (77.96–89.81)	86.56 (80.41–89.09)	0.9[a]
Body plethysmography parameter, unit	**Baseline visit (*n* = 6) Median (IQR)**	**6 weeks (*n* = 6)**	**18 weeks (*n* = 6)**	***p***
RV, *z* score	5.28 (3.06–6.92)$^{0-1,\ 0-2}$	1.81 (−1.04–3.86) $^{0-1}$	1.07 (0.01–1.81) $^{0-2}$	**0.007**[b]
RV, l	1.72 (1.21–2.09)$^{0-1,\ 0-2}$	1.13 (0.64–1.22) $^{0-1}$	0.82 (0.69–1.05) $^{0-2}$	**0.01**[b]
TLC, *z* score	2.2 (1.51–3.78)$^{0-1,\ 0-2}$	0.52 (−0.24–1.12) $^{0-1}$	0.21 (−0.36–0.76) $^{0-2}$	**0.01**[b]
TLC, l	3.31 (2.92–3.76)	2.7 (2.55–3.6)	2.49 (2.47–3.76)	0.12[a]
RV% TLC, *z* score	6.05 (2.41–8.03)$^{0-1,\ 0-2}$	2.75 (−1.3–5.29)$^{0-1}$	1.48 (0.19–2.5)$^{0-2}$	**0.01**[b]
RV% TLC, %	48.48 (35.55–57.35)$^{0-1,\ 0-2}$	35.89 (20.94–46.74)$^{0-1}$	31.36 (26.78–35.49)$^{0-2}$	**0.01**[b]
FRC, *z* score	7.07 (3.53–9.85)	3.52 (1.05–5.2)	3.04 (1.65–4.02)	**0.04**[b]
FRC, l	2.46 (2.02–2.74)$^{0-1}$	1.84 (1.63–1.99)$^{0-1}$	1.81 (1.56–2.31)	**0.04**[b]
sRaw, *z* score	6.6 (4.76–13.01)$^{0-1,\ 0-2}$	4.13 (2.88–5.47)$^{0-1}$	4.64 (2.44–5.2)$^{0-2}$	**0.01**[b]
sRaw, kPa·s	1.51 (1.24–2.46)$^{0-1,\ 0-2}$	1.15 (0.96–1.34)$^{0-1}$	1.22 (0.9–1.3)$^{0-2}$	**0.01**[b]
Impulse oscillometry parameter, unit	**Baseline visit (*n* = 11) Median (IQR)**	**6 weeks (*n* = 11)**	**18 weeks (*n* = 11)**	***P***
R5, *z* score	1.27 (0.08–1.89)$^{0-1,\ 0-2}$	0.1 (−0.54–0.7)$^{0-1}$	0.31 (−0.37–0.75)$^{0-2}$	**0.009**[b]
R5, kPa/(l/s)	1.15 (0.78–1.32)$^{0-1,\ 0-2}$	0.95 (0.68–1.02)$^{0-1}$	0.84 (0.66–1)$^{0-2}$	**0.008**[b]
R20, *z* score	−0.72 (−1.1 to −0.46)	−1.09 (−1.83 to −0.82)	−0.98 (−1.36 to −0.25)	0.02[a]
R20, kPa/(l/s)	0.51 (0.42–0.61)	0.43 (0.37–0.5)	0.47 (0.45–0.55)	0.12[b]
R5–R20, kPa/(l/s)	0.58 (0.33–0.68)	0.47 (0.27–0.57)	0.26 (0.23–0.52)	**0.002**[b]
X5, *z* score	0.4 (0.06–0.58)	1.05 (−0.28–3.01)	0.74 (−0.02–1.58)	0.18[b]
X5, kPa/(l/s)	−0.22 (−0.32 to −0.15)	−0.13 (−0.22 to −0.08)	−0.13 (−0.25 to – 0.09)	0.15[b]
Fres, *z* score	1.86 (1.26–2.6)	1.33 (0.53–2.18)	1.78 (1.29–2.08)	0.15[b]
Fres, l/s	25.34 (20.44–27.15)	20.87 (19.08–25.88)	22.75 (21.24–24.67)	0.13[b]
AX, kPa/l	4.69 (3.04–5.79)$^{0-1,\ 0-2}$	3.27 (1.91–3.75)$^{0-1}$	2.43 (1.6–3.77)$^{0-2}$	**0.0005**[b]

Note: Statistically significant values (<0.05) are showen in bold. Data are presented as the median and interquartile range.

Abbreviations: AX, reactance area; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; Fres, resonant frequency; FVC, forced vital capacity; IQR, interquartile range; n, number; R20, resistance at 20 Hz; R5, resistance at 5 Hz; RV, residual volume; sRaw, specific airway resistance; TLC, total lung capacity; X5, reactance at 5 Hz

[a]Friedman test.

[b]ANOVA test.

$^{0-1}$Significant difference between evaluation at baseline visit and evaluation after therapeutic intervention one ($p < 0.05$ post hoc test).

$^{0-2}$Significant difference between evaluation at baseline visit and after therapeutic intervention two ($p < 0.05$ post hoc test).

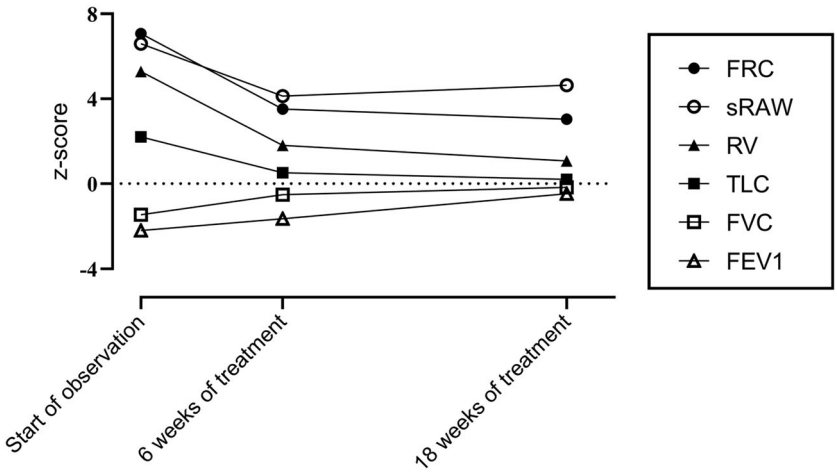

FIGURE 3 Improvement of lung function over time. FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; RV, residual volume; sRaw, specific airway resistance; TLC, total lung capacity

treatment probably reduced air trapping in the distal airways, which considerably affected the FVC and indirectly the FEV_1. In agreement with previous reports, we observed a decrease in R20–R5 and AX values. Such a change in impulse oscillometry parameters is probably also indicative of the improvement of the peripheral airways' function.[32,39]

We can speculate that the improvement in pulmonary function, resulting in better ventilation of the distal airways has contributed to the reduction in the severity of symptoms. Improved patency caused by reduced airway resistance caused an increase of vital capacity and had a noticeable impact on the patients' clinical status.

Several limitations must be considered when interpreting our findings. First, this investigation was a nonrandomized and uncontrolled observational analysis. Thus, although it seems that the improvement of PTI symptoms and PFT results was mainly related to bronchodilators, the study design with a stepwise approach does not allow to definitively link the therapeutic effect with the class of inhaled medications. In consequence, the lack of randomization and a control group significantly reduced the strength of the conclusions drawn. Second, although we managed to include a relatively large group of patients with this rare disorder, only a part of them was able to perform PFT. Even though it was an objective obstacle associated with a young age of children, it may result in a suboptimal statistical analysis power. Third, the duration of the observation was only 18 weeks. As PTI is a chronic disease and symptoms persist for years, more extended observation of patients would be justified.

In conclusion, we suggest that symptomatic children with PTI may benefit from inhaled bronchodilators and corticosteroids. Before recommendations on routine treatment of infants and children with PTI can be made, a randomized control trial to demonstrate such therapy's effects unequivocally should be done and maybe encouraged by our results.

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AUTHOR CONTRIBUTIONS

Honorata Marczak: conceptualization (equal); data curation (lead); formal analysis (equal); methodology (equal); writing original draft (equal); writing review and editing (equal). **Joanna Peradzynska**: formal analysis (supporting); methodology (supporting); writing original draft (supporting); writing review and editing (supporting). **Elias Seidl**: conceptualization (equal); data curation (equal); methodology (equal); writing review and editing (supporting). **Matthias Griese**: conceptualization (equal); methodology (equal); supervision (lead); writing original draft (equal); writing review and editing (equal). **Tomasz Urbankowski**: formal analysis (supporting); software (lead). **Joanna Lange**: conceptualization (supporting); methodology (supporting); writing review and editing (supporting). **Stanislaw Boguslawski**: data curation (supporting); methodology (supporting). **Katarzyna Krenke**: conceptualization (equal); formal analysis (equal); methodology (equal); supervision (lead); writing original draft (equal); writing review and editing (lead).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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