PEDIATR RESPIR J Vol. 2(4), 162-170, 2024

RESEARCH ARTICLE

Lung function trajectories in asthmatic children after the onset of omalizumab

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ABSTRACT

Children with severe asthma are at risk of long-term lung function impairment. In those receiving biologic treatments such as omalizumab (OZ), the medium-term evolution of lung function has shown variability.

In this retrospective single-center study, we recorded data, including lung function, from asthmatic children who started on OZ between 2012 and 2015, with at least two follow-up visits over a period of no less than two years. We determined the course of forced expiratory volume in 1 s expressed as percentage predicted (FEV_1%) in each patient by constructing the annual slope and testing the significance of its trend (positive = improvement, negative = loss, or null). Pre-bronchodilator (pre-BD) and post-BD FEV_1% slopes were determined.

The 71 children included (55 male, 57 atopic) had been started on OZ at a mean age of 11.7 (2.9), when the mean dose of inhaled corticosteroids treatment (ICS) was 1245 (856) µg/day. Asthma disease was poorly or partially controlled in 37 and 24 children, respectively. During the follow-up (mean 5.7 (2.1) years), the majority of children did not modify their pre-BD or post-BD FEV_1% slopes (59, 83%, 95% CI: 72%-91%, and 57, 80%, 95% CI: 69%-89%, respectively). Meanwhile, clinical asthma control significantly improved ($P < 0.0001$) and the ICS dose significantly decreased to 906 (649) µg/day ($P = 0.01$).

In conclusion, the real-life long-term evolution of lung function in children with severe asthma started on OZ is stable. This is accompanied by improved clinical asthma control and a reduction in the burden of ICS treatment.

HIGHLIGHTS BOX

What is already known about this topic? Omalizumab improves clinical symptoms of asthma in children, but consistent improvement in lung function has not been persistently observed. **What does this article add to our knowledge?** We demonstrate that in children with improved asthma symptoms after starting omalizumab, lung function does not significantly change despite a reduction in inhaled corticosteroid dosage. **How does this study impact current management guidelines?** Physicians managing children on omalizumab treatment must closely monitor lung function, including bronchial responsiveness, while reducing treatment to ensure there is no impairment during therapy.

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10.56164/PediatrRespirJ.2024.62

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KEY WORDS
Pediatric asthma; spirometry; bronchodilator, biologics.

INTRODUCTION

Asthma is the most common chronic disease in children, with a prevalence of 11%-13.7% in those over 6 years old in our country (1). However, only 5% of children with asthma experience severe asthma (2).

Severe asthma is defined by asthma which requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy (3). Children with severe asthma are prone to more symptoms and frequent exacerbations, which have an established deleterious effect on lung function (4). The challenges in treating these children are to decrease symptoms and exacerbations and preserve their lung function. In a cohort of children followed for asthma of various levels of severity, it has been found that over 10 years, 28% of cases had a decrease in lung function, as assessed by a significant negative slope of their Forced Expiratory Volume in 1 second (FEV_1) over time (5).

The recent availability of biologics, such as omalizumab (OZ), to treat severe asthma in children has shown positive effects in the rate of hospitalizations and the dose of ICS (decrease), as well as in asthma control and lung function (improvement) (6). However, the outcomes of randomized controlled trials conducted in highly selected and closely monitored patients are not always similar to those measured in real-life settings. The few studies exploring the long-term lung function outcomes (1 to 3 years) in children receiving OZ have failed to constantly detect an improvement in FEV_1, Forced Vital Capacity (FVC), and their ratio (2, 7-10). This is an important issue, as physicians following these children need to know what lung function evolution is to be expected. In this retrospective study, we evaluated a cohort of children routinely tested for lung function in the same laboratory using standardized procedures, before and at least twice after the start of OZ, to determine the proportion of children who had a significant change in FEV_1.

MATERIALS AND METHODS

Study design

We designed a retrospective single-center study at Armand Trousseau Hospital in Paris, France, involving children who had been started on OZ between 2012 and 2015 for moderate to severe uncontrolled asthma. The decision to start OZ was made after a multidisciplinary discussion.

The criteria for initiating OZ treatment in asthmatic children at our institution are as follows: exclusion of differential diagnoses, management of modifiable factors and comorbidities, use of a high daily dose of ICS (based on age and medication, as outlined by Global Initiative for Asthma (GINA, ginasthma.org)), completion of patient therapeutic education, presence of positive TH2 inflammatory markers, and symptomatic asthma with a high annual dose of oral corticosteroids and/or uncontrolled asthma symptoms at each visit.

Subjects

Inclusion criteria were a typical clinical history of asthma symptoms with, at least once, a bronchial obstruction showing a significant reversibility on the lung function test. The children must have had at least three spirometry during the follow-up (the first one just before or within 3 months after OZ treatment onset). Non-inclusion criteria were a less-than-2 year of period of OZ treatment or a lack of clinical data on asthma control.

Data collection

Once the patient was included, we recorded anthropometric data, history of atopy and of asthma, previous lung function tests, allergenic sensitization, asthma comorbidities, and treatment before OZ start. Lung function tests included forced spirometry performed at baseline and 20-minute post-bronchodilator (BD) (400 µg of salbutamol administered via a metered dose inhaler through a spacer device) using a bodyplethysmograph (BodyBox®, Medisoft™, Sorinnes, Belgium) that was calibrated daily, in accordance with current international recommendations at the time of the test (11). In practice, after entering the patient's age, sex and height into the software, the patient was fitted with a nose clip and connected to the mouthpiece. The patient then performed a deep inspiration followed by a forced exhalation through the pneumotachograph. At least three tests were conducted to obtain at least two reproducible maneuvers, both at baseline and after bronchodilation, from which the best FVC and FEV_1 values were recorded. Post-bronchodilation reversibility in FVC or

FEV_1 was considered significant if it reached at least 12% of the baseline value. The results were expressed as z-scores and percentages predicted according to the Global Lung Initiative reference values (12).

We recorded annual visits, including clinical assessments and lung function tests contained in the patient's electronic records. Asthma control over the past four weeks was assessed using the four-question tool recommended by GINA: 1) were daytime asthma symptoms present more than twice a week? 2) was there any night waking due to asthma? 3) was a short-acting beta-adrenergic reliever used for symptoms more than twice a week (excluding reliever taken before exercise)? 4) was there any activity limitation due to asthma? Patients with all negative responses were considered to have good asthma symptom control, those with one or two positive responses had partial asthma symptom control, and those with three or four positive responses had poor asthma symptom control. Patients and their family were informed about the potential use of their data in a retrospective study and provided consent. The study was approved by the Institutional Review Board of the French Société de Pneumologie de Langue Française (CEPRO 2024-043).

Statistical analysis

To study the course of FEV_1% overtime, we determined for each patient the slope of the annual change in FEV_1 percent predicted using standard least squares linear regression models and performed Pearson test to classify the slope (significant when $P < 0.05$). The slope was deemed as positive (improvement in lung function) when the slope was significantly positive, and negative (loss or insufficient growth of lung function) when the slope was significantly negative. When Pearson test P-value was not significant, the slope was considered null (stable lung function).

Results were numbers (percentages, %) for categorical data, and mean (standard deviation, SD) or median (25^{th}-75^{th} percentiles) according to the normality or not of their distribution. Between-group comparisons were performed using the student test or the Mann-Whitney U test. Categorical variables were compared using the Chi-square test or the Fisher exact test. Only children with a baseline lung function recorded before the start of OZ were included in the lung function comparisons, while the construction of FEV_1% trajectories also included those whose first lung function was recorded within 3 months after the start of OZ.

Results with a P-value < 0.05 were considered as significant. Statistical analyses were performed using GraphPad Prism® (v 6.07, Boston, MA) and Octave.

RESULTS

Among the 104 patients identified as having started OZ during the study period, 71 fulfilled the inclusion criteria (**Figure 1**). The study population included 55 male and 16 female patients. A family history of atopy was present in 41 patients (58%). Personal atopic

Table 1. *Lung function before onset of OZ and at last visit in 71 study patients.*

	Before OZ	Last visit
Age, years	10.5 (2.6)	16.6 (2.1)
Height, cm	141.6 (16)	169.1 (12.2)
Asthma symptom control		
Good	2	39 *
Partial	24	28
Poor	37	4
Daily dose, µg/day beclomethasone-equivalent	1245 (856)	906 (649) **
Baseline spirometry		
FEV_1 (L)	1.77 (0.57) †	3.22 (0.68)
FEV_1 (%predicted)	87.2 (15.9)	88.5 (14.5)
FEV_1 (z-score)	-1.07 (1.32)	-0.94 (1.25)
FVC (L)	2.42 (0.81)	4.30 (1.02)
FVC (%predicted)	102.6 (14.1)	103.0 (13.3)
FVC (z-score)	0.19 (1.17)	0.20 (1.15)
FEV_1/FVC	0.74 (0.11)	0.77 (0.13)
FEV_1/FVC (z-score)	-1.80 (1.25)	-1.72 (1.27)
Post-bronchodilator spirometry		
FEV_1 (L)	2.01 (0.61) †	3.36 (0.8)
FEV_1 (%predicted)	95.6 (13.7)	95.2 (13.8)
FEV_1 (z-score)	-0.33 (1.15)	-0.37 (1.19)
FVC (L)	2.53 (0.82)	4.28 (1.0)
FVC (%predicted)	104.2 (13.1)	102.8 (12.8)
FVC (z-score)	0.33 (1.08)	0.19 (1.11)
FEV_1/FVC	0.81 (0.09)	0.84 (0.08)
FEV_1/FVC (z-score)	-0.97 (1.23)	-0.89 (1.20)

OZ: Omalizumab; FEV_1: Forced Expiratory Volume in 1 s; FVC: Forced Vital Capacity. Results are mean (SD) or number; †: in 67 patients before OZ treatment. Different from before OZ; * $P < 0.0001$; ** $P = 0.01$.

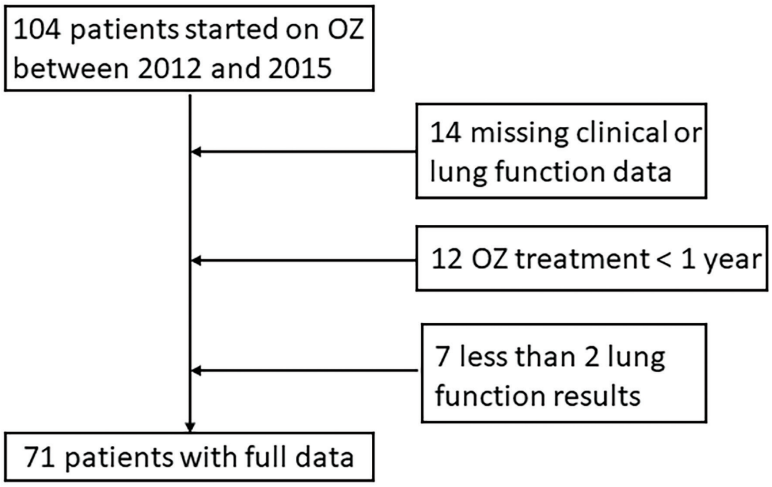

Figure 1. *Participant flow chart. OZ: Omalizumab.*

conditions were documented as follows: atopic dermatitis in 36 patients (51%), rhino-conjunctivitis in 59 patients (83%), and food allergy in 23 patients (32%). The age at asthma onset was under 3 years for 44 patients (62%), between 3 and 6 years for 10 patients (14%), and after 6 years for 6 patients (8%). The mean (SD) age at the start of OZ treatment was 11.7 (2.9) years. All but two patients received a high dose of ICS, with a mean (SD) daily dose of 1245 (856) µg in beclomethasone equivalents.

Age, asthma control, lung function and treatment on the first and last visit (before and last follow-up after OZ onset) are shown in **Table 1**. Mean (SD) follow-up was 5.7 (2.1) years, with a maximum of 9.8 years. Asthma control significantly improved, and ICS dose significantly decreased with OZ treatment, but FEV_1 z-score did not change between measurements at baseline and at last OZ treatment visit.

The majority of patients did not modify their slope of FEV_1% (null slope in 59 (83%, 95% CI: 72%-91%) for pre-BD FEV_1; 57 (80%, 95% CI: 69%-89%) for post-BD FEV_1) (**Table 2**). In **Figure 2** shows the individual significant positive and negative FEV_1% slopes for pre-BD (**Figure 2A**) and post-BD (**Figure 2B**) among all the FEV_1% predicted values recorded. The slope of pre-BD and post-BD FEV_1% was significantly positive in 8 and 3 patients, respectively, and negative in 4 and 11 patients, respectively. No patient exhibited a discrepancy

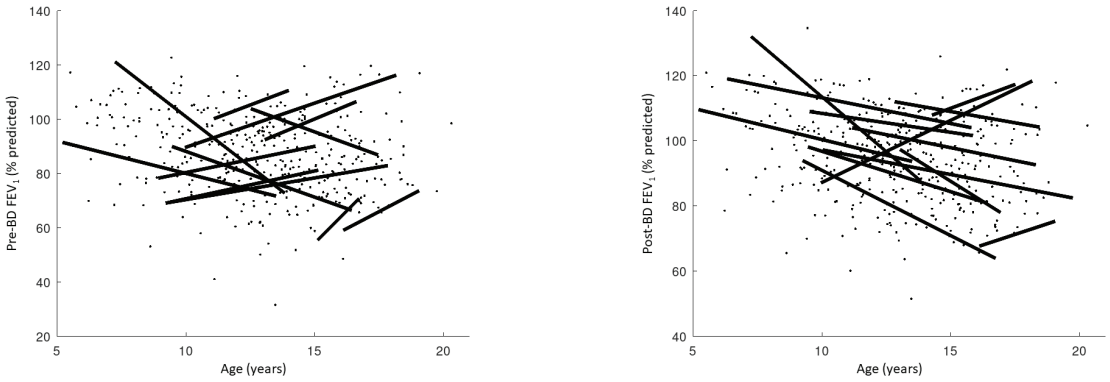

Figure 2*. (**a**) Pre-bronchodilator FEV_1 measured in 71 before and after omalizumab onset; (**b**) post-bronchodilator FEV_1 measured in 71 before and after omalizumab onset. The dots represent pre-bronchodilator FEV_1 (**a**) and post-bronchodilator FEV_1 (**b**) measurements expressed as percentage predicted and performed in all the study patients. Only the significantly positive (n = 8, **Figure 2a**, n = 3, **Figure 2b**) and negative (n = 4, **Figure 2a**, n = 11, **Figure 2b**) slopes are represented by solid lines. FEV_1: Forced expiratory volume in 1 second.*

Table 2. *Lung function across the three groups of patients according to the pre-bronchodilator FEV_1% slope.*

	Positive slope	Null slope	Negative slope
Number of patients	8	59	4
Sex Male/Female	5/3	46/13	4/0
Duration of OZ treatment (years)	5.3 (2.2)	5.0 (4.6)	7.5 (2.6)
		Results at OZ onset	
Age (years)	11.6 (2.8)	10.3 (2.4)	9.0 (3.4)
Height (cm)	144.9 (9.5)	141.8 (16.0)	134.0 (22.3)
Baseline spirometry			
FEV_1 (L)	1.64 (0.47)	1.80 (0.56)	1.68 (0.96)
FEV_1 (%predicted)	73.6 (16.2)	88.5 (15.4)	94.8 (9.2)
FEV_1 (z-score)	-2.18 (1.30)	-0.96 (1.28)	-0.36 (0.7)
FVC (L)	2.29 (0.46)	2.45 (0.84)	2.11 (1.14)
FVC (%predicted)	90.9 (15.7)	103.9 (13.7)	107.1 (3.1)
FVC (z-score)	-0.82 (1.34)	0.31 (1.13)	0.54 (0.24)
FEV_1/FVC	0.72 (0.14)	0.75 (0.10)	0.79 (0.09)
FEV_1/FVC (z-score)	-2.00 (1.65)	-1.79 (1.22)	-1.47 (0.99)
Post-bronchodilator spirometry			
FEV_1 (L)	1.86 (0.43)	2.04 (0.62)	2.05 (0.97)
FEV_1 (%predicted)	83.4 (14.6)	97.8 (12.9)	101.3 (7.2)
FEV_1 (z-score)	-1.39 (1.23)	-0.19 (1.08)	0.13 (0.55)
FVC (L)	2.40 (0.53)	2.55 (0.85)	2.42 (1.11)
FVC (%predicted)	95.0 (19.1)	105.6 (11.9)	106.3 (3.6)
FVC (z-score)	-0.48 (1.58)	0.45 (0.98)	0.50 (0.27)
FEV_1/FVC	0.78 (0.12)	0.81 (0.09)	0.84 (0.08)
FEV_1/FVC (z-score)	-1.31 (1.61)	-0.94 (1.18)	-0.60 (1.25)

OZ: Omalizumab; FEV_1: Forced Expiratory Volume in 1 s; FVC: Forced Vital Capacity. Results are mean (SD) or number.

between a positive pre-BD FEV_1% slope and a negative post-BD FEV_1% slope, or vice versa. In the largest group of 11 patients with a significant negative post-BD FEV_1% slope, only three also had a negative pre-BD FEV_1% slope. The post-treatment clinical asthma control was similar in these three children compared to the eight children with a null pre-BD FEV_1% slope (totally controlled in three and six children, respectively, partially controlled for the two remaining children).

There was no relationship between the FEV_1 outcome and the personal history of atopy or the amount of ICS received before OZ treatment. **Figure 3** describes the distribution of FEV_1% slopes according to baseline lung function. A positive FEV_1% slope was more frequently observed in children with low baseline z-score of FEV_1.

DISCUSSION

In this retrospective single-center study on lung function trajectories in asthmatic children after the onset of OZ, we found that in 83% of cases, the slope of pre-BD FEV_1% was null, despite significant improvement in asthma symptom control and reduction in ICS dosage. The real-life evolution of lung function in children after the onset of OZ treatment has been scarcely evaluated, with conflicting results. The two studies in which FEV_1 did not improve were based on small populations (n = 14 and 17) and, therefore, may lack statistical power (7, 9). The two largest studies (n = 48 and 78) finding a statistical improvement in FEV_1 evaluated the change in lung function over a relatively short period (6 and 12 months) compared to the usual duration of OZ treatment (2, 10). However, none of these studies eval-

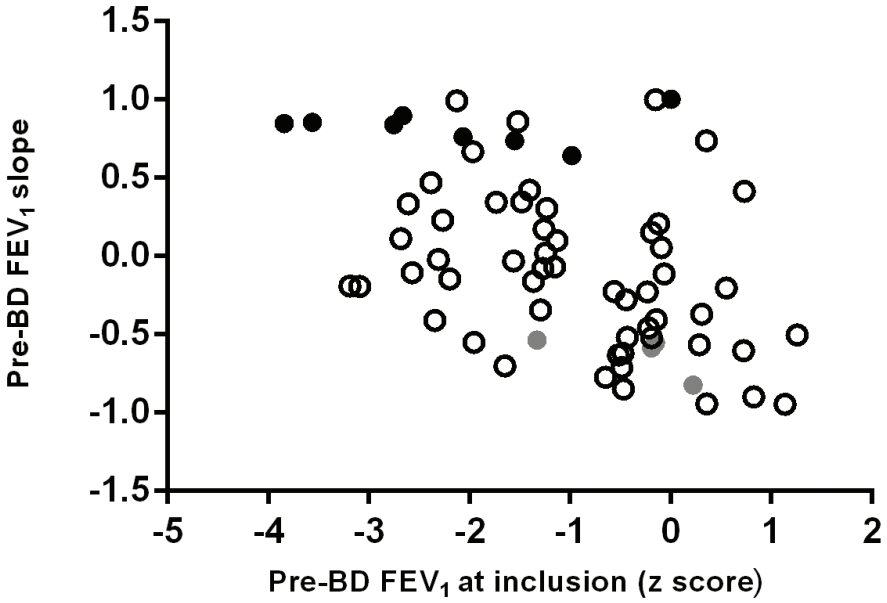

Figure 3. *Distribution of pre-bronchodilator FEV_1% slopes according to FEV_1 at inclusion. Black circles represent patients with a positive slope, open circles represent patients with null slope, grey circles represent patients with a negative slope.*

uated the slope of FEV_1% after OZ onset. In our study, FEV did not improve significantly after at least 2 years of follow-up (**Table 1**), consistent with the progression of individual FEV% slopes Indeed, we found that, in most cases, the slope of FEV_1% was not significant, with no difference between pre- and post-BD results.

One of the challenges is to define the significance of FEV_1% change over time. The wide range of definitions used in the literature to define significant variations in FEV_1 needs to be addressed, especially in children, in whom lung growth prevents comparisons between absolute values of FEV_1 or FVC. One recent proposal is the use of the conditional change score for FEV_1 (13). This score has the advantage of taking into account the age of the subject, the natural variability of FEV_1 in healthy subjects and the interval between the two measurements. Using a methodology similar to ours for calculating individual slopes of FEV_1% in asthmatic adolescents and adults (standard least-squares linear regression models), Delinger *et al*. defined the significance of changes as severe decline (>2% loss/year); mild decline (>0,5-2,0% loss/year); no change (0,5% loss/year to <1% gain/year); and improvement (≥1% gain/year) (14). On the other hand, we chose to use a statistical test (Pearson's) to determine the significance of the individual slopes. Using this methodology, Mahut and colleagues previously showed in a study of 295 asthmatic children not receiving OZ treatment, each with at least 10 spirometry tests, that 28% exhibited a negative FEV_1% slope, while 69% had a null slope (5). This proportion of asthmatic children losing lung function over time was the same as that observed in the CAMP study (28% *versus* 26%) (15). Our study therefore shows that children receiving OZ experienced less lung function loss than those not receiving this treatment (5, 15).

The second important factor to consider in our population is that ICS dosage significantly decreased in the children receiving OZ treatment, likely because of clinical improvement in their asthma. This can be seen as a positive effect of OZ on lung function, even though most children had a null FEV_1% slope. However, data on ICS treatment doses should be interpreted with caution, as treatment compliance has been found to be low in this population. In 79 asthmatic adults treated with OZ, after 2 years of treatment, low compliance with ICS treatment was noted in 40 patients (taking less than 80% of the ICS prescribed), 26 of whom took less than 50% of the prescribed dose of ICS (16). These non-compliant patients showed greater improvement in asthma control and quality of life, which could explain lower treatment adherence.

The last finding related to lung function was that children with a positive pre-FEV_1% slope tended to have a low z-score of FEV_1 at inclusion, while the few ones with negative slope had a higher z-score of FEV_1 at inclusion (**Figure 3**). This result is consistent with the study by Mahut and colleagues, where significantly higher baseline FEV_1 in children with a negative slope was accompanied by a higher FEV_1/FVC ratio, which should serve as a warning sign when treating these patients (5). There were too few patients with a negative pre-BD FEV_1% slope to perform statistical analysis in our study, and we cannot infer from our results why children with higher baseline FEV_1/FVC values would be likely to decline further.

The trend indicating a higher frequency of negative slopes for post-BD FEV_1% compared to pre-BD FEV_1% slopes (11 *versus* 3) should not be overinterpreted, given the small sample size and the retrospective nature of the study. But eight of these patients had a null pre-BD FEV_1% slope. This may indicate a poor prognosis associated with initially high bronchial responsiveness to bronchodilators (large post-BD FEV_1 change) in some patients. This should be examined in more detail, as the follow-up of the Dunedin cohort has shown that relapses, persistence, or severity of symptoms were more common among those exhibiting the greatest responsiveness to bronchodilators (17, 18).

Our study has many limitations because of its retrospective design. We excluded 33 children from the study: 12 were ineligible due to discontinuation of OZ treatment at the six-month visit because of lack of efficacy, and 21 did not meet the inclusion criteria for clinical and lung function follow-up. Of these, 14 were alternately followed in the hospital and in private practice (missing data), and seven were unable to perform sufficiently reliable spirometry. These exclusions are not expected to introduce bias, as neither the physician's location nor the patient's inability to complete spirometry at certain visits corresponds to any specific lung function pattern. We were unable to record treatment compliance, but in this real-world study, it is likely that some patients did not take the full dose of their treatment, particularly those who experienced significant improvements in asthma control and quality of life. In our study, children with a negative FEV_1% slope had a similar asthma control to that of the rest of the population and may therefore have been similarly compliant. However, there is no solid evidence supporting the notion that ICS treatment can prevent lung function decline in asthmatic children (15).

This is a single-center study, so our results may differ from other centers. However, patients are referred from all over the district to decide whether to initiate OZ treatment and most of them benefit from joint follow-up by their local carers and our severe asthma clinic. The advantage of this single-center study is that lung function tests were performed using the same machines and methodology by a team of trained technicians adhering to international recommendations. Furthermore, all lung function test results were consistently reported in a single database.

CONCLUSIONS

The real-life evolution of lung function in asthmatic children treated with OZ is stable in most cases, which contrasts with the observed improvement in clinical symptoms. However, we also found a less frequent significant loss of lung function compared to previous reports on children with asthma of varying severity who were not receiving OZ (5, 15).

The potential decrease of bronchodilator responsiveness in some patients with a negative post-BD FEV_1% slope, in conjunction with the clinical and functional evolution, would be better studied in a systematic prospective study.

ACKNOWLEDGMENTS

We are grateful to Jessica Assouline, Michèle Boulé, Houda Guillo, Marc Koskas, Marie-Claude La Rocca, Fatma Lacin, Lucia Maingot, and Noria Medjahdi for their help in supervising the children's lung function tests, and to Claire Goaguen, Pascale Jacquemart, Fanny Koëth, Valérie Le Bail, Hélène Morsy †, Isabelle Schmitt, and Françoise Vallée for their technical assistance, all working in Unité d'Exploration Fonctionnelle Respiratoire, Armand Trousseau Hospital, Paris, France.

† Sadly, Helène Morsy passed away during this study.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

Financial support

There was no institutional or private funding for this article.

Author contributions

CLT and NB designed the study and recorded the data. PB, BM and CD performed the slopes calculation and statistics. CLT, PB and NB drafted the manuscript. BM and CD made important comments on the manuscript. All Authors gave approval of the final version.

Ethical approval

Human studies and subjects

the study received the approval of the Institutional Review Board of the French Société de Pneumologie de Langue Française (CEPRO 2024-043).

Animal studies

N/A.

Data sharing and data accessibility

The Authors confirm that the data supporting the findings of this study are available within the article.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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