Estimating the minimal important difference in FEV_1 for patients with allergic bronchopulmonary aspergillosis

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To the Editor:

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic lung disorder caused by immunological reactions targeted against *Aspergillus fumigatus* colonising the airways of asthma and cystic fibrosis patients [1]. If undiagnosed or inappropriately treated, the inflammatory process can progress perpetually, culminating in end-stage respiratory disease. Oral glucocorticoids are the treatment of choice in ABPA; antifungal triazoles are good alternatives [2]. Treatment response in ABPA is assessed using a composite of clinical symptoms, serum total IgE, chest radiograph and spirometry [3]. Notably, the minimal important difference (MID) for forced expiratory volume in the first second (FEV_1) in ABPA remains unknown. The MID is the smallest change that the patients perceive as beneficial. In the current study, we aimed to estimate the MID for FEV_1 in patients with ABPA complicating asthma.

We performed a retrospective analysis of data collected (January 2012 to July 2017) during three randomised controlled trials [4–6], and included subjects randomised in the oral prednisolone arm. The institute ethics committee approved the study protocol. We obtained written informed consent from all the study subjects.

We included subjects with treatment-naïve acute-stage ABPA complicating asthma according to the following criteria. The subjects had both the following: 1) immediate cutaneous hyperreactivity on *Aspergillus* skin test or *A. fumigatus*-specific IgE levels >0.35 $kUA \cdot L^{-1}$; and 2) elevated serum total IgE levels >1000 $IU \cdot mL^{-1}$; and two of the following: 1) presence of precipitating antibodies (or IgG >27 $mgA \cdot L^{-1}$) against *A. fumigatus* in serum; 2) peripheral blood eosinophil count >1000 μL^{-1}; 3) chest radiographic abnormalities consistent with ABPA; and 4) bronchiectasis on computed tomography of the chest. We excluded subjects with any of the following: 1) intake of systemic glucocorticoids or triazoles for >3 weeks in the preceding 6 months; 2) concomitant use of medications, including voriconazole, inhaled amphotericin B, omalizumab, or other biological agents; 3) uncontrolled diabetes mellitus, chronic renal failure, chronic liver failure, and immunosuppressive drugs; and 4) pregnancy.

We retrieved the following information from our records: 1) baseline demographic data, including age, sex, and others; 2) baseline immunological investigations and imaging data; and 3) spirometry and serum total IgE measurements at baseline and 6 weeks after treatment. We calculated the difference between post-treatment (6 weeks) and baseline FEV_1 values (absolute values and percentage change). The percentage change was calculated as ((FEV_1 at 6 weeks − FEV_1 at baseline)/FEV_1 at baseline)×100.

All the subjects received oral prednisolone sequentially at a dose of 0.5 $mg \cdot kg^{-1} \cdot day^{-1}$, 0.25 $mg \cdot kg^{-1} \cdot day^{-1}$ and 0.125 $mg \cdot kg^{-1} \cdot day^{-1}$ for 4 weeks each. The drug was tapered by 5 mg every 2 weeks and discontinued after 4 months. At 6 weeks, we monitored the patient with a physical examination review, chest radiograph, serum total IgE and spirometry. We defined response to treatment as an improvement in cough and dyspnoea (>75% of baseline), partial (⩾50%) or total clearance of chest radiographic lesions (if present before treatment), and decline in serum total IgE values by >25% after 6 weeks of treatment. Inhaled corticosteroids, long- and short-acting β_2-agonists, and montelukast were used for asthma control at the treating physician's discretion.

Shareable abstract (@ERSpublications)
This study found a minimal important difference of 158 mL (or 17%) for the FEV_1 in patients with acute-stage allergic bronchopulmonary aspergillosis complicating asthma treated with prednisolone https://bit.ly/3JvfBmI

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The study's primary outcome was to estimate the MID of FEV_1 for assessing treatment response (at 6 weeks) in subjects with acute-stage ABPA.

We performed statistical analysis using the commercial statistical package SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA; IBM Corp.). The differences between repeated measurements at baseline and 6 weeks were assessed using Wilcoxon rank-sum test. We used both distribution and anchor-based methods to determine the MID for FEV_1. We used the change in serum total IgE at 6 weeks as an external anchor. Further, three categories (no change, minimal and more than minimal) were created based on the change in serum total IgE (<26%, 26–50%, >50%) [7]. We used the external anchor only if the Pearson correlation coefficient between the FEV_1 difference and the external anchor was >0.3 [8, 9]. The MID for anchor-based methods was calculated by subtracting the median value of the FEV_1 (baseline minus 6 weeks) in the "no change" from the "minimal change" category [10]. If an external anchor did not meet the *a priori* criterion for validity, we used distribution-based methods for estimating the MID. For distribution-based methods, we used: 1) standard deviation method: standard deviation of the difference of test–retest FEV_1 scores/2; and 2) standard error method: standard deviation of the difference of test–retest FEV_1 scores/$\sqrt{2}$. There is no consensus on choosing between the MID derived using the standard deviation and the standard error methods. As a result, we have averaged the values obtained from the two methods [7–9].

TABLE 1 Baseline characteristics of the study population (n=182) and estimation of the minimal important difference (MID) for the forced expiratory volume in the first second (FEV_1) using distribution-based methods

Parameter	Baseline	After treatment for 6 weeks	p-value
Clinical features			
Age, years	34 (25–45)		
Male/female, n	85/97		
Height, cm	161 (155–169)		
Weight, kg	53 (45–62)		
Duration of asthma, in years	9 (4–16)		
Haemoptysis	62 (34.1)		
Expectoration of mucus plugs	36 (19.8)		
Spirometry			
FEV_1, L	1.77 (1.26–1.33)	2.07 (1.56–2.60)	<0.0001
FVC, L	2.58 (1.95–3.35)	2.78 (2.30–3.62)	<0.0001
FEV_1/FVC	66.4 (57.1–76.6)	72.0 (62.8–79.6)	<0.0001
Immunological tests			
Type 1 *Aspergillus* skin test	166 (91.2)		
Aspergillus precipitins	78 (42.9)		
A. fumigatus-specific IgE, kUA·L^{-1}	30.8 (16.1–50.3)		
Total IgE, IU·mL^{-1}	8812 (4534–13 892)	3834 (2335–6936)	<0.0001
Total eosinophil count, cells·μL^{-1}	900 (330–1761)		
A. fumigatus-specific IgG, mgA·L^{-1}	74.8 (46.9–140.5)		
Imaging			
Fleeting opacities on chest radiograph	89 (48.9)		
Bronchiectasis	175 (96.2)		
Number of lung segments affected by bronchiectasis	8 (5–12)		
Centrilobular nodules	58 (31.9)		
Presence of HAM	75 (41.2)		
Asthma treatment			
ICS dose (BDPE), µg	400 (250–500)		
Formoterol dose, µg	12 (12–24)		
Montelukast use	62 (34.1)		

Variable	SD method	SE method	Average
FEV_1, mL	130	185	157.5
FEV_1, %	14.2	20.2	17.2

All values are presented as n (%) or median (interquartile range), unless otherwise stated. Standard deviation (SD) method: standard deviation of FEV_1 values at baseline minus 6 weeks/2. Standard error (SE) method: standard deviation of FEV_1 values at baseline minus 6 weeks/$\sqrt{2}$. *A. fumigatus*: *Aspergillus fumigatus*; BDPE: beclomethasone dipropionate equivalent; FVC: forced vital capacity; HAM: high-attenuation mucus; ICS: inhaled corticosteroids; IgE: immunoglobulin E; IgG: immunoglobulin G.

We included 182 treatment-naïve ABPA subjects with a mean±SD age of 38±15 years; 85 were men. The subjects had asthma for a median duration of 9 years. The baseline spirometry values, immunological investigations, imaging findings and therapy received for underlying asthma are summarised in table 1. A majority (96.2%) of the subjects had bronchiectasis with a median of eight bronchopulmonary segments affected. All the subjects received inhaled glucocorticoids at a median dose of 400 $\mu g \cdot day^{-1}$ (beclomethasone dipropionate equivalent) and long-acting β2-agonist, formoterol, at a median dose of 12 $\mu g \cdot day^{-1}$ for asthma control.

All the subjects showed a response to therapy at 6 weeks. The Pearson correlation coefficient for the change in FEV_1 value *versus* the change in serum total IgE was 0.14. As the external anchor did not meet our pre-specified criteria for validity, we derived the MID for FEV_1 using the two distribution-based methods (table 1). The standard deviation of the test–retest FEV_1 values (baseline minus 6 weeks) was 0.261. The MID for FEV_1 by the standard deviation and the standard error method was 130 mL and 185 mL, respectively, with a mean of 157.5 mL. Similarly, the MID for FEV_1 (%) by the standard deviation and the standard error methods was 14.2% and 20.2%, with a mean of 17.2%.

The present study is the first to evaluate MID for FEV_1 in patients with ABPA. We suggest a MID of 158 mL (or 17%) for FEV_1 in assessing treatment response in acute-stage ABPA complicating asthma. While MID is most useful in patient-reported outcomes, the MID for FEV_1 is also likely useful in clinical trials. There are few published data on the MID for FEV_1 in adult asthmatic patients [11]. In a study of 281 adult patients with mild-to-moderate asthma, the authors reported the MID for FEV_1 as the mean change in FEV_1 in patients rating themselves as "a little better" on the global rating of change in asthma [12]. The MID for FEV_1 was 230 mL or a 10.4% change from baseline. Contrarily, the MID for FEV_1 in COPD patients has been suggested as 100–140 mL [13, 14]. The FEV_1 change following treatment in acute-stage ABPA would closely resemble the change in FEV_1 seen in asthmatic patients, as many patients with acute-stage ABPA have uncontrolled asthma.

Our study has a few limitations. The current study was a retrospective analysis of data from a single centre. Due to the retrospective nature, we did not record the global rating of change in the patient's improvement that could have provided a simpler alternative to serum IgE as an external anchor. While the sample size was relatively large we could use only the distribution-based methods, as the external anchor did not satisfy our pre-defined reference for correlation. Although both anchor- and distribution-based methods have limitations, the former is preferred [15]. Alternatively, the MID could also be established using a Delphi consensus. Finally, the MID for FEV_1 derived from the current study applies only to acute-stage ABPA complicating adult asthma. The MID values cannot be extrapolated to relapsing or steroid-dependent stages of ABPA.

In conclusion, we found a MID of 158 mL (or 17%) for the FEV_1 in patients with acute-stage ABPA complicating asthma treated with prednisolone. A more extensive prospective study using a global rating of change in the patient's symptoms is required to confirm our results.

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