Impulse Oscillometry versus Spirometry in a Long-Term Study of Controller Therapy for Pediatric Asthma

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Abstract

Background—Determination of the benefits and limitations of specific physiologic tests has not been well studied in long-term clinical pediatric trials.

Objective—To determine the utility of impulse oscillometry in a long-term comparison of three controller regimens in children with persistent asthma.

Methods—Children 6 to 14 years of age with mild to moderate persistent asthma were characterized with oscillometry and spirometry before entry into a clinical trial and then serially during 48 weeks of therapy with either an inhaled corticosteroid, a combination inhaled corticosteroid with a long-acting beta-agonist, or a leukotriene receptor antagonist.

Results—The FEV_1/ FVC ratio as well as the FEF_{25-75} in terms of spirometric parameters and the reactance area (XA) from impulse oscillometry appeared to complement information provided

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Clinical Implications: Assessment of respiratory mechanics over time with impulse oscillometry may offer important information about the pulmonary response of asthmatic patients to therapy that is not reflected by spirometric parameters.

by FEV_1 when comparing the tests and factors that appeared to predict a response to treatment. Reactance area was unique in that it, as distinct from spirometric variables, reflected ongoing improvement during the latter part of the trial. In general, improvements in XA during the latter part of the study occurred independent of indices of atopy and the level of airway responsiveness.

Conclusion—Assessment of respiratory mechanics over time with oscillometry may offer additional insights into response of asthmatic patients to therapy. In particular, the pattern of improvement seen in XA over the course of therapy suggests this test may detect alterations in airway mechanics not reflected by spirometry. The possibility that changes in reactance area reflect ongoing improvement in small airway function deserves additional study.

Keywords

pediatric asthma; impulse oscillometry; spirometry; therapy of asthma

INTRODUCTION

The ability to easily evaluate respiratory function in children with asthma is of central importance in terms of following the course of disease. This is especially important when tracking the effects of therapy.[1] With respect to asthma clinical research, physiologic tests are commonly used to define the effects of intervention. While a variety of tests may be utilized, values obtained from spirometry are most commonly reported due in part to the large volume of information on the use of tests such as FEV_1. However, this approach may have limitations. For example, spirometric tests may be less helpful than other measures of respiratory function when assessing airway lability in preschool children at risk for persistent asthma.[2] Thus, the issue of what physiologic tests will be most informative in long-terms studies requires evaluation.

Forced oscillation is one of several techniques that have been used to obtain measures of respiratory function in subjects with lung disease.[3,4] This method involves the application of pressure waves to the airway opening via a mouthpiece, and measuring respiratory system impedance from which resistance and reactance can be derived.[5] Results from studies to date suggest a reasonable agreement with more traditional measures of lung function in children with asthma.[6] In this respect, there are reports of use of this technique in young children with acute asthma.[7,8] This technique has also been used to quantify the response to methacholine[6,7,9,10] and histamine[9] challenges in young asthmatics. The results of these and other studies as reviewed by Oostveen et al[3] and Goldman[5] suggest forced oscillation may have advantages when evaluating acute responses to therapy and may also prove useful in following the course of the disease.

The focus of this work is on a comparison of spirometric measures with values obtained by impulse oscillometry (IOS) as methods to follow the course of children with asthma that have been treated in differing ways. The latter is a forced oscillation technique that involves application of a rectangular pulse signal to the airways.[11] Subjects assessed were participants in the clinical trial entitled the "Pediatric Asthma Controller Trial" (PACT).[12] This study utilized a cohort of children with mild to moderate persistent asthma enrolled to compare the effectiveness of 3 treatment regimens in achieving asthma control. Performance

of spirometry and IOS before, during, and at the end of the trial allowed comparison of differing ways of monitoring respiratory function over a prolonged period of therapy.

METHODS

Study Population

The study population for the PACT trial has been described.12 Briefly, children with asthma ages 6 to less than 14 years of age were screened, characterized, and randomized at 5 clinical centers of the Childhood Asthma Research and Education (CARE) Network funded by the National Heart, Lung, and Blood Institute (NHLBI). PACT was designed to compare the effectiveness of 3 treatment regimens in achieving asthma control in school-aged children with mild-moderate persistent asthma. Inclusion criteria included physician-diagnosed asthma, the ability to perform reproducible spirometry, and an FEV_1 (measured more than 4 hours since use of a bronchodilator) of at least 80% predicted normal at screening and at least 70% predicted at randomization. Each child had airway lability as defined by methacholine responsiveness with a PC_{20} 12.5 m g/ ml (see below). Exclusion criteria included systemic corticosteroid use within 4 weeks prior to enrollment. Two or more hospitalizations or 4 or more courses of systemic corticosteroids in the past year also precluded participation. A listing of inclusion and exclusion criteria has been presented.12 Informed consent consisted of signing a copy of the consent form approved by the Institutional Review Board of the subject's respective study institution . Assent from the child was also obtained.

Protocol

All participants had mild-moderate persistent asthma, as defined by diary-reported symptoms, beta-agonist use or peak flows obtained during the final week of a 2 to 4 week run-in period. After run-in, participants were assigned to one of three treatment arms: fluticasone 100 mcg morning and 100 mcg evening (Flovent Diskus®, GlaxoSmithKline) plus placebo oral drug in the evening (fluticasone monotherapy); fluticasone 100 mcg/ salmeterol 50 mcg (Advair Diskus®, GlaxoSmithKline) in the morning and salmeterol 50 mcg (Serevent Diskus®, GlaxoSmithKline) in the evening plus placebo oral drug in the evening (PACT combination); or placebo Diskus® in the morning and placebo Diskus® in the evening plus montelukast 5 mg (Singulair®, Merck) in the evening (montelukast monotherapy). Treatment assignment followed a double-blind, randomized parallel group design, stratified by center.

Pulmonary Function Testing: Spirometry and IOS

Spirometry and IOS were performed by CARE-certified technicians with over-reading performed to insure quality control. The tests were performed using a pneumotachograph-type spirometer interfaced with a personal computer system (Jaeger-Toennies GmbH, Hoechberg, Germany). Equipment and testing procedures for the maximal expiratory flow volume (MEFV) maneuvers met American Thoracic Society (ATS) 1994 Spirometry standards13,14 with techniques modified for children less than 8 years of age as described by Eigen et al 15 and Arets et al.16 Age, gender, and ethnicity appropriate prediction equations were used to calculate percent of predicted values for spirometric parameters.17

IOS was performed by applying a rectangular pulse signal to airways with a pressure step wave every 250 milliseconds through a loudspeaker to the airway opening via a mouthpiece through which the subjects breathed normally (tidal breathing) for 30 seconds at a time (see below). The subject wore a nose clip during sampling with the subject or parent/ guardian gently holding the sides of the face to decrease the shunt compliance of the cheeks. Repeated measurements took a few minutes to perform, with at least 3 IOS procedures performed both before and after bronchodilator. Measurements were made using commercially available equipment (Master Screen, E. Jaeger, Würzburg, Germany) and were processed on a Dell computer. Measurements were carried out during stable tidal breathing over a 30 second interval of time with the indices obtained being the total respiratory resistance (R) and reactance (X) as a function of frequency. The former was calculated from pressure and flow signals where pressure was in phase with flow while the latter computation involved pressure out of phase with flow. Reactance at low frequencies reflects the pressures needed to overcome the viscoelastic properties of the lung. In addition to resistance and reactance, the resonant frequency (Fres) was recorded. This is the frequency at which reactance is zero. Also recorded was the reactance area (XA), an integrated response index for reactance developed by Goldman 5 reflecting the integral of the negative values of X from 5 Hz to Fres. This value may in part reflect small airway function. The duration of each measurement was 30 seconds, yielding a total of 120 impulses from which the mean values of R and X were calculated at discrete frequencies from 5 to 35 Hz. During data acquisition, pressure and flow traces were graphically displayed in real time. Measurements were accepted when the tracings showed uninterrupted breathing during data acquisition. Measurements were rejected if disturbed by coughing, breathholding, swallowing, or vocalization. The values from 3 acceptable 30-second periods of data collection were averaged in terms of IOS parameters. The value of R_{10} was monitored to assess repeatability of the 30 seconds of data collection. The coherence values at 10 Hz had to be   0.80 while values of R_{10} had to be within a 20% range (calculated from the largest value for R_{10}). Predicted values for R_5, R_{10}, X_5 and Fres are from Lechtenbörger et al (unpublished communication) based on 614 healthy children and adolescents from 5 to 17 years of age. These values represent the default normal reference values for the equipment used in this study. For XA, normal values for children of the age range employed in this study have not been established. Thus, the latter is reported as an absolute value with changes tracked over the course of the study. For XA, improvement is reflected by a decrease in this value.

Methacholine Challenge

A CARE-certified technician measured airway responsiveness by the decrease in FEV_1 after administering increasing concentrations of methacholine (Provocholine®, Methapharm, Coral Springs, Fl). This drug was delivered by the small volume nebulizer-tidal breathing technique (Wright nebulizer, Medi-tech Ltd, Montreal, Quebec) according to a standardized procedure18 and ATS 2000 methacholine challenge testing guidelines.19 The test was performed at least 4 hours after the last use of a short-acting bronchodilator and/ or caffeine consumption, and at least 4 weeks after the last oral corticosteroid use or respiratory tract infection. Baseline FEV_1 values equaled or exceeded 70% of predicted prior to the test. A diluent step was performed and utilized as the reference value for calculation of PC_{20}.

Measurement of Biomarkers

Exhaled nitric oxide (eNO) was measured employing the online technique recommended by the American Thoracic Society[20] using the NIOX® system (Aerocrine AB, Stockholm, Sweden). This technique is described by Strunk et al.[21] Measurement of eNO was obtained prior to spirometry. Peripheral blood eosinophil counts were obtained by automated assay at each center. Immediate hypersensitivity skin tests were performed with 8 common aeroallergens as outlined previously.[21] Testing was performed in accordance with a study specific protocol.[22,23]

Statistical Analysis

Given the time course and pattern of the responses to therapy in terms of FEV_1 and FEV_1/FVC as reported in the PACT trial[12] and reproduced in part in Figures 1 and 2 (dashed lines), a regression model with a change point at 12 weeks was used to describe changes in lung function over time. The term "change point" refers to the time at which the temporal profile of the outcome changes. In this case, the form of the regression model is a straight line from time zero to 12 weeks, connected to another straight line extending from 12 to 48 weeks (Figure 1; regression model shown by straight lines with change point at 12 weeks). All outcomes were defined in terms of change from baseline and thus, the regression line begins at zero on the y-axis. The slope of the line from baseline to 12 weeks represents the initial response to treatment while the slope of the line from 12 to 48 weeks represents later changes following the initial response.

The regression models were fit within the framework of repeated measures analysis for longitudinal data.[24] The results of the regression models are presented as population averages, unadjusted for other covariates. Residual analysis was performed to verify that the model was appropriate for the data. All analyses were performed using SAS Version 9.2 statistical software. Significance was established at $p < 0.05$, 2-tailed.

Protocol Review

An Institutional Review Board at each center plus an NHLBI Protocol Review Committee and an NHLBI Data Safety Monitoring Board approved the PACT protocol. The latter committees were formed specifically for the CARE Network.

RESULTS

Demographics /Clinical Characteristics of Study Participants

Demographic characteristics were presented by Sorkness et al.[12] Of the 285 randomized subjects, 252 completed the study. The three treatment groups were well matched, with characteristics at baseline of mild-to-moderate asthma. Of the scheduled visits, 97% were completed. Adherence to study medications was high as presented in the main outcome paper.[12] In terms of the primary outcome (asthma control days), fluticasone monotherapy and PACT combination were comparable and superior to montelukast.

Spirometry and IOS Results

As presented in the original manuscript, prebronchodilator FEV_1 (% predicted) and FEV_1/ FVC (expressed as a percent) increased significantly more with fluticasone monotherapy than with PACT combination and montelukast monotherapy. The mean change in FEV_1 % predicted from baseline was 6.32% with fluticasone monotherapy and 3.62% with PACT combination while the mean change for FEV_1/ FVC was 3.95% and 1.76% respectively. Montelukast did not improve theses measure of lung function.

The results of fitting the FEV_1 and FEV_1/ FVC data to the change-point model are shown in Figure 1. The associated parameter estimates are summarized in Tables I and II. The parameter estimates represent the changes in FEV_1 and FEV_1/ FVC per week. The p-values reported in Table I are those associated with testing whether the slope parameter for each treatment is different from zero. The p-values in Table II are those associated with testing whether the treatments have equal slopes. Over the first 12 weeks of therapy, the slopes for these measures of airways obstruction were significant in a positive direction for combination and fluticasone therapy (Table I) with all groups differing from the two others (Table II). However, the pattern over the last period of therapy (12–48 weeks) was different. Slopes for both tests of lung function were close to zero with the probabilities not significant. Thus, these measures of lung function improved initially in two of the three treatment arms and then were fairly static for the remainder of the study.

Changes over time for $FEF_{25–75}$ (expressed as a percent of predicted) for all 3 treatment groups are shown in Figure 1C. The statistical analysis in terms of the slopes and comparisons between groups is presented in Tables I and II respectively. Over the first 12 weeks of therapy, the slopes for this measure of airways obstruction were significant in a positive direction for combination and fluticasone therapy (Table I) and significant in a negative direction for the montelukast group. During this initial period of treatment, the groups receiving combination and fluticasone therapy were significantly different from the group receiving montelukast (Table II). Once again, the pattern over the last period of therapy (12–48 weeks) was different. Slopes were close to zero with the probabilities not significant. Thus, $FEF_{25–75}$ improved initially in two of the three treatment arms and then was fairly static for the duration of the study for all treatment arms.

For XA, the patterns of change over time were different than those seen with spirometric parameters. The changes in absolute value of XA for the three treatment groups are shown graphically in Figure 1D while the slopes and their estimates for the first and second phases of treatment are listed in Table I. During the initial 12 weeks of therapy, the only group in which the slope was significantly different than zero was the one receiving combination therapy. During the subsequent 36 weeks of treatment, the group receiving fluticasone showed significant improvement as reflected by the negative slope for change in XA over time (Table I), with the differences between the fluticasone group and the other two groups being significant (Table II).

Relationship of Biomarkers and Level of Reactivity to Changes in XA

The possibility of correlations existing between potential biomarkers of disease and the variable (XA) that improved with fluticasone therapy during the latter part of the study was also addressed. Listed in E Table I of the Online Repository are the slopes of XA during the latter part of therapy for subjects treated with fluticasone. The subjects were divided into those with eNO values of less than 25 versus those with values of 25 or higher, subjects with negative versus those with positive skin tests, and participants with eosinophil percentages on their blood counts of less than 4% versus those with values of 4% and higher. As listed in E Table I, the slope estimates and the probabilities were comparable in all groups with the exception of the grouping taking into consideration eosinophil percentages in blood. In this analysis, those that would be considered to have a biomarker compatible with more active disease had a slope estimate that was significant. When eNO or skin test reactivity were used to define the sub-groupings, statistical significance was found regardless of eNO levels or whether the subjects had reactions to aeroallergens.

In addition to the three biomarkers, the subjects receiving fluticasone were also assessed in terms of slope estimates and probabilities depending on their methacholine responsiveness. For this analysis, subjects were divided into those with a PC_{20} less than 2.0 mg/ ml and those with a value equal to or greater than 2.0 mg/ ml. As seen in E Table I, the p values were both significant. The slope estimates were greater and the probabilities greater in the group that was less reactive in terms of methacholine responsiveness.

DISCUSSION

Assessment of lung function with IOS was easily accomplished in children with persistent asthma who were 6 to 14 years of age. This study found one IOS parameter (XA) demonstrated continued improvement over a prolonged period of time compared to spirometric variables. As such, IOS may offer a valuable adjunct to spirometry in following the course of subjects enrolled in clinical studies. In terms of biomarkers, a higher level of circulating eosinophils identified subjects more likely to respond in terms of improvements in XA with inhaled corticosteroid therapy. Elevated eNO, skin test reactivity to aeroallergens, and the level of airway responsiveness did not distinguish those with improvements in XA.

The value of assessing objective measures of lung function that include spirometric parameters in children with asthma is well established. For example, Bye et al [25] argued that failure to perform spirometry in children with asthma results in underdiagnosis of airflow obstruction. More recently, Fuhlbrigge and colleagues[26] demonstrated a strong association between FEV_1 expressed as a percent of predicted and the risk of an asthma attack over the subsequent year. In terms of clinical research in asthma, spirometric variables are commonly used to define entry criteria and to gauge the effects of intervention. However, use of FEV_1 may have limitations in terms of both clinical care and research. In this respect, the question has been raised about whether FEV_1 is the best spirometric measure of severity in childhood asthma.[27,28] Thus, the issue of what physiologic tests other than FEV_1 will be of use in following the course of subjects with persistent asthma over a prolonged period of treatment was a focus of this work.

The design of the PACT study provided a unique opportunity to compare methods of physiologically characterizing school-age children with persistent asthma over time when they were treated with three distinct medical regimens. These children were characterized by respiratory physiology, symptom burden, and methacholine responsiveness. The study design also allowed assessment of biomarkers in subjects so that changes in physiologic measurements could be compared to markers of disease activity when therapy began.

In terms of spirometry, we focused on FEV_1 as well as the ratio of FEV_1 to FVC and FEF_{25-75} for reasons given previously. While the initial report of the results of this study focused on both FEV_1 as well as FEV_1/FVC,[12] we felt it important to address the changes over time in more detail with a random effects model that addresses both acute and more chronic changes over time. Our focus in this analysis on FEF_{25-75} was based on the argument that this test as well as FEV_1/FVC may more accurately measure lung function impairment than FEV_1 in children. The former parameter (FEF_{25-75}) has been felt to possibly reflect small airway function[29,30] and this also had appeal in terms of our analysis. Reactance area, which reflects the integrated sum of the negative reactance values below the resonant frequency, is also felt to reflect at least in part peripheral airway function.[5,31] Thus, our analysis yielded information on spirometric variables that may be useful in gauging response, but also on a spirometric parameter as well as an IOS parameter that may reflect events within more peripheral airways.

Our analysis of these tests of lung function demonstrated important trends in terms of therapeutic responses. For FEV_1 as well as FEV_1/FVC and FEF_{25-75}, significant changes in slopes were limited to the first 12 weeks of therapy with the improvements maintained but not significantly increasing over the latter part of treatment. The improvements were seen in the groups receiving fluticasone monotherapy and combination therapy. For XA, the pattern was different. For this test, only the group receiving combination therapy exhibited a change in slope that was significantly different from zero in the initial 12 weeks of treatment. In addition, during the subsequent 36 weeks of treatment, the group receiving fluticasone showed significant improvement as reflected by the negative slope of XA over time (Table I) with the differences between the fluticasone and other two groups being significant (Table II).

Comment is necessary regarding the changes that occur in XA over time when the results are expressed in absolute units rather than as a percent of predicted. This IOS parameter is a reflection of both the resonant frequency and X_5. Both parameters normally decrease with growth, and thus XA is also expected to normally decrease in value over time with linear growth. However, as noted previously, predicted values of XA for children over the range of ages and heights used in this study are not available. Thus, we elected to use absolute values instead of extrapolated normal values from other data sets. With this approach, the question must be asked if the changes seen with fluticasone therapy only reflect changes that occur with growth over the period of study. This is unlikely for several reasons. First, as reported by Sorkness et al,[12] differences among the three therapies in this study in terms of growth effects were not significant, including when stratified for age. Comparable growth was seen in all three treatment groups over the course of treatment, ranging from a mean of 5.3 cm in the fluticasone monotherapy and combination therapy groups to 5.7 cm in the montelukast

monotherapy group. Second, during the last 36 weeks of treatment, the group receiving fluticasone showed not only a significant improvement as reflected by the negative slope for change in XA over time (Table I), but a significant difference in slope when compared to the other two groups (Table II). Third, if stature had been significantly impaired in the groups receiving inhaled corticosteroids, changes in XA values over time would be expected to be less and not greater in magnitude. Therefore, for these reasons, we believe that the changes in XA over time in the corticosteroid monotherapy group reflect more than just alterations that normally occur with growth.

Both FEF_{25-75} and XA may reflect events within more peripheral airways. Yet, these two measures differed in terms of the patterns of improvement seen during the study. This was especially evident in terms of the improvement seen with corticosteroid monotherapy for XA but not FEF_{25-75} during the latter part of therapy. Thus, XA may be more sensitive to alterations in peripheral airway function than the former. Another possibility is that the improvement in XA over time reflects not only small airway function, but other mechanical events within the lung. Unfortunately, other tests of airway function that might shed light on this issue were not part of this study. More information on what is occurring over time in terms of air trapping as reflected by the residual volume and ratio of residual volume to total lung capacity might be helpful. Use of quantitative computed tomography might also help assess events within peripheral airways.[30]

In older children, the CARE Network has previously reported that treatment of mild - moderate asthma in subjects 6 to 17 years of age with an inhaled corticosteroid led to not only improvement in spirometry but also to significant improvement in R_5 and XA.[32] While resistance measures at various frequencies including R_5 and R_{10} were obtained by IOS during PACT and analyzed as part of this work, the changes were not of similar magnitude or as consistent as those seen with XA (CARE Network, unpublished observations). Thus, we focused on XA alone for this report.

Biomarkers that reflect an atopic state have been used to determine if they help predict the response to therapy. In another CARE network study, a favorable response (in terms of FEV_1) to 8 weeks of fluticasone therapy was associated with higher baseline (pretreatment) levels of eNO, total eosinophils counts, and levels of serum IgE.[33] In terms of biomarkers used in PACT, only peripheral eosinophil percentages identified subjects more likely to respond in terms of improvements in XA with inhaled corticosteroid therapy. Improvements in XA were seen regardless of eNO levels and skin test responses. Improvements in XA also occurred independent of the level of airway responsiveness. This observation also differed from the previous study where improvement in FEV_1 was associated with an initially lower PC_{20} (greater airway reactivity) to methacholine.[33] These observations suggest improvements seen in XA with corticosteroid therapy over time may reflect effects that occur independent of atopy.

These data suggest that IOS may be informative in longer-term studies and may reflect improvements in lung function not reflected by spirometric parameters. This latter concept is supported by other studies. In adults with asthma, Evans and colleagues [34] suggested that IOS is a more sensitive measure of change in airway function than spirometry when

assessing the response to room temperature and cold temperature exercise challenges. In older children with asthma, Goldman et al 35 found significant differences in some IOS parameters (including both R_5 measured during inspiration and XA) but not spirometric indices when assessing adolescents daily over a period of three days. In preschool children, Marotta et al2 reported that IOS responses to bronchodilator demonstrated significantly greater change than observed with FEV_1 in those 4-year-old children most likely to have persistent asthma. Conventional spirometry did not establish similar statistically significant findings. Thus, IOS might provide a u seful d iagnostic tool when monitoring for the development of early asthma. In addition, IOS might also be helpful in obtaining objective outcome measures in studies of early intervention when spirometric measures are not as easily obtained.36 Both issues require additional study in preschool children with wheezing that may progress to chronic asthma.37

In summary, analysis of the response of PACT participants to an ICS, combination therapy, and a LTRA using IOS was feasible, and revealed differences in the time course of improvement compared with spirometric variables. Additional investigations to define benefits and limitations of this method of physiologic assessment over prolonged periods of time appear justified. In addition, additional study to address the possibility that the changes seen in XA in this study reflected continuing improvement in small airway function deserves attention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

ATS	American Thoracic Society
CARE	Childhood Asthma Research and Education Network
eNO	exhaled nitric oxide
FEF_{25-75}	forced expiratory flow from 25 to 75% of forced vital capacity
FEV_1	volume (liters) of air expired in the first second of forced expiration
Fres	resonant frequency
FVC	forced vital capacity
Hz	Hertz (cycles per second)
ICS	inhaled corticosteroids
IOS	impulse oscillometry

LABA	long-acting beta-agonist
LTRA	leukotriene receptor antagonist
MDI	metered dose inhaler
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
PACT	Pediatric Asthma Controller Trial
PC_{20}	methacholine dose that decreases FEV_1 by 20%
PEF	peak expiratory flow
R_5, R_{10}	resistance of the respiratory system at 5 and 10 Hz
X_5	reactance of the respiratory system at 5 Hz
XA	reactance area

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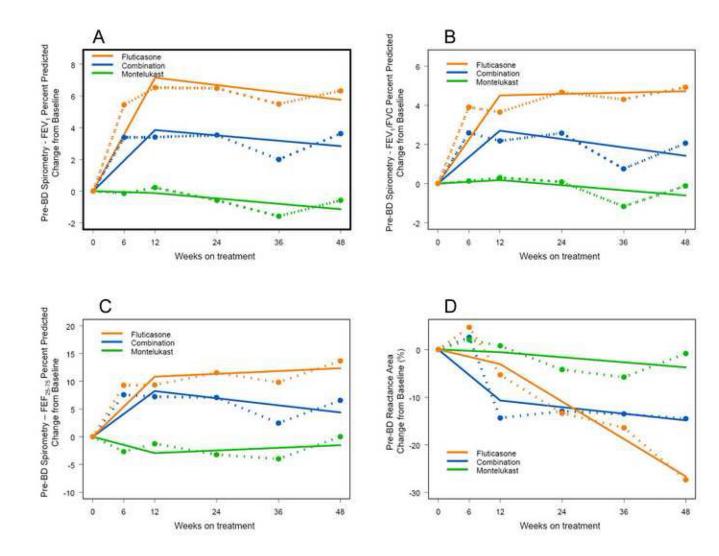
FIG 1.
Changes in FEV_1 (A), FEV_1/ FVC (B), FEF_{25-75} (C), and XA (D) over time are displayed for three treatment groups as both mean data at each measurement point (dashed lines) and as a regression model with a change point at 12 weeks (solid lines). The statistical analyses using the regression model are summarized in Tables I and II. Over the first 12 weeks of therapy, the slopes for FEV_1, FEV_1/ FVC, and FEF_{25-75} were significant in a positive direction for combination and fluticasone therapy. However, for these spirometric parameters, the pattern over the last period of therapy (12–48 weeks) was different with all slopes close to zero. Conversely, XA significantly improved in the fluticasone group during the latter period as reflected by the negative slope for change in XA.

TABLE I

Slopes for tests of lung function in first 12 weeks and from 12 to 48 weeks of treatment

Lung Function	Time	Treatment	Estimate (95% CI)	Probability
FEV$_1$	0–12 weeks	Combination	0.320 (0.201, 0.439)	<0.0001
		Fluticasone	0.596 (0.477, 0.715)	<0.0001
		Montelukast	−0.011 (−0.128, 0.107)	0.8589
	12–48 weeks	Combination	−0.028 (−0.096, 0.039)	0.4138
		Fluticasone	−0.039 (−0.105, 0.027)	0.2483
		Montelukast	−0.028 (−0.094, 0.038)	0.4010
FEV$_1$/FVC	0–12 weeks	Combination	0.225 (0.135, 0.315)	<0.0001
		Fluticasone	0.375 (0.287, 0.463)	<0.0001
		Montelukast	0.015 (−0.071, 0.101)	0.7323
	12–48 weeks	Combination	−0.036 (−0.086, 0.015)	0.1693
		Fluticasone	0.006 (−0.043, 0.055)	0.8140
		Montelukast	−0.022 (−0.070, 0.026)	0.3753
FEF$_{25-75}$	0–12 weeks	Combination	0.686 (0.461, 0.910)	<0.0001
		Fluticasone	0.902 (0.671, 1.134)	<0.0001
		Montelukast	−0.245 (−0.477, −0.012)	0.0393
	12–48 weeks	Combination	−0.107 (−0.235, 0.022)	0.1044
		Fluticasone	0.042 (−0.087, 0.171)	0.5238
		Montelukast	0.040 (−0.090, 0.169)	0.5483
XA	0–12 weeks	Combination	−0.893 (−1.544, −0.242)	0.0073
		Fluticasone	−0.256 (−0.889, 0.378)	0.4293
		Montelukast	−0.047 (−0.697, 0.603)	0.8876
	12–48 weeks	Combination	−0.116 (−0.484, 0.253)	0.5394
		Fluticasone	−0.656 (−1.008, −0.303)	0.0003
		Montelukast	−0.088 (−0.451, 0.274)	0.6325

TABLE II

Differences in slopes for tests of lung function in the first 12 weeks and from 12 to 48 weeks of treatment

Lung Function	Time	Treatment	Estimate (95% CI)	Probability
FEV$_1$	0–12 weeks	C vs. F	−0.275 (−0.443, −0.107)	0.0014
		C vs. M	0.331 (0.164, 0.499)	0.0001
		F vs. M	0.606 (0.439, 0.774)	<.0001
	12–48 weeks	C vs. F	0.011 (−0.084, 0.105)	0.8247
		C vs. M	0.000 (−0.094, 0.094)	0.9988
		F vs. M	−0.011 (−0.104, 0.083)	0.8237
FEV$_1$/FVC	0–12 weeks	C vs. F	−0.150 (−0.276, −0.024)	0.0199
		C vs. M	0.210 (0.086, 0.335)	0.0010
		F vs. M	0.360 (0.237, 0.483)	<.0001
	12–48 weeks	C vs. F	−0.041 (−0.112, 0.029)	0.2489
		C vs. M	−0.014 (−0.084, 0.056)	0.7008
		F vs. M	0.028 (−0.041, 0.096)	0.4292
FEF$_{25–75}$	0–12 weeks	C vs. F	−0.217 (−0.539, 0.106)	0.1887
		C vs. M	0.930 (0.607, 1.254)	<.0001
		F vs. M	1.147 (0.819, 1.475)	<.0001
	12–48 weeks	C vs. F	−0.149 (−0.331, 0.033)	0.1099
		C vs. M	−0.146 (−0.329, 0.036)	0.1162
		F vs. M	0.002 (−0.180, 0.185)	0.9803
XA	0–12 weeks	C vs. F	−0.637 (−1.546, 0.271)	0.1694
		C vs. M	−0.846 (−1.766, 0.074)	0.0717
		F vs. M	−0.209 (−1.116, 0.699)	0.6522
	12–48 weeks	C vs. F	0.540 (0.030, 1.050)	0.0382
		C vs. M	−0.027 (−0.544, 0.490)	0.9184
		F vs. M	−0.567 (−1.073, −0.062)	0.0281

[*] C = Combination; F = Fluticasone; M = Montelukast