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Predicting Response to Inhaled Corticosteroid Efficacy (PRICE Trial)

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Abstract

Background—Although guidelines recommend anti-inflammatory therapy for persistent asthma, recent studies suggest that 25-35% of asthmatics may not improve lung function with inhaled corticosteroids.

Objective—To evaluate potential biomarkers of predicting short term (6-week) response to inhaled corticosteroid with subsequent evaluation of responders and non-responders to asthma control over a longer interval (16 additional weeks).

Methods—Eighty-three asthmatic subjects off steroid were enrolled in this multi-center study. Biomarkers and asthma characteristics were evaluated as predictors of inhaled corticosteroid response over a six week trial for changes in FEV_1 and methacholine PC_{20}. Following this, an additional four month trial evaluated asthma control.

Results—Although multiple baseline predictors had significant correlations with improvements for short term inhaled steroid success, the only strong correlations ($r \geq \pm 0.6$) were albuterol reversibility ($r=0.83$, $p<0.001$); FEV_1/FVC ($r=-0.75$, $p<0.001$); and FEV_1 % predicted ($r=-0.71$, $p<0.001$). Dividing the subjects in the short term inhaled steroid trial into responders (> 5% FEV_1 improvement), and non-responders (≤ 5%) determined the longer term need for steroids. For the non-responders, asthma control remained unchanged whether inhaled corticosteroids were continued or were substituted with a placebo, $p=0.99$. The good short term responders maintained asthma control longer term only if maintained on inhaled steroids ($p=0.007$).

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Conclusion—The short term response to inhaled corticosteroids with regard to FEV_1 improvement predicts long term asthma control.

Capsule Summary—A six week trial of ICS, in patients not currently on steroids, producing a ≥ 5% improvement in FEV_1 can predict long term asthma control and the need for continued steroid use.

Keywords

inhaled corticosteroids; predicting response; therapy; characteristics; biomarkers

INTRODUCTION

Inhaled corticosteroids (ICS) are the preferred anti-inflammatory therapy for the treatment of persistent asthma as recommended by both national and international guidelines (1-4). However, an increasing number of studies have demonstrated marked variability in response to ICS with 25-35% of asthmatic subjects showing little improvement in FEV_1 and/or bronchial hyperresponsiveness (BHR) (5-7). In the recent Gaining Optimal Asthma Control ("GOAL") study, Bateman and colleagues used increasing doses of combination therapy with an ICS and long acting β_2-agonist for a one year duration which included a short oral corticosteroid trial (8). While asthmatics of different severities (defined by ICS dose at enrollment) showed a differential response to this treatment (a smaller proportion of the more severe asthmatics responded than the milder asthmatics), approximately 30% of the entire subject group enrolled did not achieve the study's standards for "well controlled asthma".

Retrospective analysis of a prior Asthma Clinical Research Network Study identified elevated fraction exhaled nitric oxide (FeNO) and greater bronchodilator reversibility to a short acting β_2-agonist as predictors of a positive FEV_1 response to ICS and higher sputum eosinophils and shorter duration of asthma (years since diagnosis) as predictors of improvement in BHR (7). This study did not examine, however, whether these responses in pulmonary function to short-term ICS treatment could predict the long term response in the maintenance of asthma control with more prolonged treatment. Thus, the Asthma Clinical Research Network embarked on a larger prospective study to analyze biomarkers and characteristics of asthma as predictors of response to short-term (6 week) ICS treatment and then to examine the relationship of the short term response to the importance of continued ICS treatment for maintenance of asthma control over a longer time interval (16 additional weeks).

METHODS

Study Population

Inclusion criteria for study subjects were asthmatic individuals between 18-55 years of age with a baseline FEV_1 55-85% predicted and a methacholine $PC_{20} \leq 12$ mg/ml. Since FEV_1 reversibility was an outcome variable, this was not used as an inclusion criteria. No ICS or systemic corticosteroids were allowed for at least 4 weeks prior to enrollment. No smoking was allowed for one year prior to enrollment and cumulative exposure was less than 10 pack-years. Other exclusion criteria included other respiratory disease or significant medical illness, respiratory infection within six weeks prior to screening, pregnancy, and prior enrollment in the above mentioned Asthma Clinical Research Network study (7). The lack of adherence to study procedures during the run-in period also mandated exclusion (see below).

Protocol review was performed by a National Heart, Lung and Blood Institute (NHLBI) Protocol Review Committee and the study was monitored by an NHLBI Data Safety

Monitoring Board. The protocol and consent were approved by each Center's Institutional Review Board and each subject gave informed, written consent.

Study design

Eighty-three subjects were enrolled into this study. After a two-week run-in characterization period, the subjects were begun on single-blind ICS, hydrofloroalkaline-beclomethasone proprionate (HFA-BDP) at 160 mcg twice daily (Figure 1). This period was to prospectively evaluate biomarkers and characteristics that would predict ICS response (FEV_1 and PC_{20} to methacholine). Biomarkers that were evaluated were β_2-agonist response, FeNO, induced sputum eosinophils, lung function, and BHR. Characteristics included duration of asthma diagnosis, age, gender, height, weight, and ethnicity. All biomarkers were obtained immediately prior to initiation of ICS and at the end of the 6-week trial.

After the single-blind period, subjects were stratified based on the FEV_1 response to ICS. Responders were defined as a > 5% FEV_1 improvement over the 6-week trial, while non-responders had ≤ 5% change. At this point, the subjects were randomized to a double-blind, placebo controlled 16-week trial (Figure 1) to evaluate asthma control by the primary outcome, the Asthma Control Questionnaire (ACQ) (9). Secondary outcomes were morning peak expiratory flow (PEF) rates, symptom free days and nights, rescue albuterol use, and exacerbations. We evaluated the PC_{20} response as a determinant of ICS dependency for maintaining asthma control and other secondary outcomes by a retrospective stratification. PC_{20} responders were defined as > 1 doubling dilution over the 6-week ICS trial and non-responders as ≤ 1 doubling dilution.

Procedure

Spirometry, methacholine challenge, FeNO, and induced sputum were performed and analyzed as in prior Asthma Clinical Research Network studies (10,11). The maximum bronchodilator reversibility (12) used an initial four actuations (360 mcg) of albuterol from a metered dose inhaler. After 15 minutes, three repeat spirometric maneuvers were performed with the best FEV_1 selected. Then two additional albuterol actuations (180 mcg) were administered followed again by 15 minutes and repeat spirometry. If the difference in improvement between the 4 and 6 actuations was < 5%, the test was terminated. If the FEV_1 rose by an additional ≥ 5% after these two additional actuations, a final 2 actuations were given. The greatest improvement from baseline was considered as the maximum bronchodilator response.

Asthma control was defined by the "mini" Asthma Control Questionnaire, i.e. the set of six questions excluding FEV_1 (9); this was chosen as FEV_1 was an independent outcome measurement. A clinically significant change in the ACQ is considered to be 0.5 units. Asthma exacerbations were defined as an increase in symptoms of cough, sputum, chest tightness, wheezing, and/or shortness of breath in association with at least one of the following: ≥ 8 rescue albuterol inhalations over baseline for 48 hours or ≥ 16 per 24 hours; decrease in peak flow to ≤ 65% of baseline on 2 of 3 consecutive scheduled measurements; FEV_1 ≤ 80% of baseline; FEV_1 < 40% predicted; or need for systemic corticosteroids (10).

Adherence monitoring was performed with a Doser™ device (Meditrak, Hudson MA) on the ICS metered-dose inhaler to electronically record the number and timing of an actuation. The Jaeger peak flow meter (Houston, TX) was used for electronic recording of peak flow date and time. Subjects needed to have electronic documentation during the run-in phase of ≥ 85% compliance with required to actuations from a placebo inhaler and ≥ 12 days of morning and evening peak flows to continue in the study.

Statistical analysis

The precision to estimate whether certain biomarkers or asthma characteristics were associated with response to ICS based on FEV_1 (FeNO and BD response) and PC_{20} (sputum eosinophils and duration of asthma) was determined based on data from our previous study (7). We determined that a sample size of 80 subjects would allow us to estimate a 95% confidence interval for Kendall's tau coefficient with width = 0.20 for each response (tau ± 0.10) (13). This sample size assumed a standard deviation of 0.4 and allowed for a maximum of 20% drop-outs.

For the 6-week ICS trial, the primary outcome variables were percent improvement in FEV_1 and the doubling dilution change in PC_{20} which were both evaluated as continuous outcomes. The association between the baseline biomarkers/characteristics and the primary outcomes was evaluated by Kendall's tau coefficient for ordinal and non-normally distributed baseline measures, and Pearson correlation coefficient for normally distributed baseline measures.

For the four-month randomized study, asthma control was measured repeatedly throughout the duration of the trial for the two treatment arms stratified by the 6-week FEV_1 response/non-response. In order to appropriately incorporate all the repeated measurements from the four month study, a stratified repeated measures analysis of covariance model was implemented to evaluate asthma control from the "mini" Asthma Control Questionnaire throughout the randomized phase of the trial. Secondary outcomes in the four month study (morning peak flow, rescue albuterol, FEV_1 % predicted, % symptom free days and nights) were also evaluated by stratified repeated measures analysis of covariance models. Results are reported in terms of model-based average values adjusted for baseline values and visits. Time to exacerbation was analyzed by Kaplan-Meier curves for the two treatment arms stratified by FEV_1 response to ICS, and treatment arms were compared via the log rank test within each level of stratification. Although the groups were stratified by the % improvement in FEV_1 during the four-month portion of the study, we were also able to retrospectively examine whether the change in PC_{20} predicted protection against loss of asthma control. Therefore, repeated measures analysis of covariance models evaluating asthma control, and survival analysis methods evaluating time to exacerbation were also used to compare the two treatment arms stratified by PC_{20} response.

The choice of > 5% as the cut-point for ICS response is supported from our analysis of this study by noting that the 5% cut-point provides a better distinction of the trend that is seen in the ICS vs. placebo comparison in the 4-month trial with respect to the asthma control outcomes. In other words, the asthma control outcomes for the ICS and placebo groups are more similar for the 5% non-responders, and more different for the 5% responders, than for another corresponding classification, 7.5%. This can be determined by evaluating the stratified ICS vs. placebo plots of the asthma control outcomes, as well as the stratified treatment comparisons from the repeated measures analysis of covariance models. The treatment effect nested within FEV_1 stratification is more significant for the 5% cut-point (p=0.026), than for the 7.5% cut-point (p=0.052). The choice of 5% is also supported from our exacerbation analysis during the 4-month trial. Using the 5% cut-point showed a more significant reduction in exacerbation rates for the ICS vs. placebo groups in the good responders defined by > 5% (p=0.028) than in the good responders defined by > 7.5% (p=0.059). This choice is also supported by the fact that it is a more conservative choice for the determination of continued ICS treatment. Using the 5% cut-point to determine who might benefit from continued ICS treatment will identify more subjects than using the 7.5% cut-point.

RESULTS

Study Population

A total of 83 subjects were enrolled with 36 males and 47 females. Thirty-eight minority (African American and Latino) individuals were enrolled. These subjects came from surrounding communities of the individual ACRN Centers and not specifically from patients seen at these testing referral centers. Of the 83 enrolled subjects, 72 completed the initial 6-week trial. The reasons for drop-out are described below. The baseline descriptive characteristics of the 72 subjects are shown in Table 1. Since asthma is a variable disease, it is difficult to categorize severity at any given time. However, all these individuals were persistent asthmatics in the moderate severity range. As a group, 57% had prior oral corticosteroid use, 61% prior ICS use, with a mean FEV1 of 72.5% predicted, 21% reversibility, ACQ score of 1.0, and methacholine PC_{20} of 0.75 mg/ml. The exclusion criteria included no inhaled or systemic corticosteroids within four weeks of enrollment. The average (range) length of time off of oral corticosteroids in 41 subjects who used this therapy was 33 (1-216) months. The length of time off ICS in 44 subjects with prior use was 27.4 (1.2-120) months.

Six Week ICS Period

Seventy-two subjects completed the 6-week trial. On ICS, 11 subjects did not complete the initial ICS 6-week study were and dropped due to: serious adverse events-2, significant asthma exacerbation-3, other exclusion criteria-2, consent withdrawn-1 and lost to follow-up-3.

The FEV_1 increased from a baseline mean ± SE of 2.62 ± 0.07 L to 2.84 ± 0.07 L ($p < 0.001$). There were 39 subjects (54%) who were ICS responders and 33 subjects (46%) non-responders. The distribution of responses can be seen in Figure 2. The responders had significantly lower % predicted FEV_1 and FEV_1/FVC ratio at baseline than the non-response group (Table 2). Sputum eosinophils or FeNO were no different between the groups (Table 2).

The PC_{20} geometric mean (coefficient of variation) at baseline was 0.76 mg/ml (1.22) and with ICS treatment was 1.11 mg/ml (1.25). The doubling dose increased by 0.60 ± 0.20 (p=0.003). There were 28 subjects (39%) that were ICS responders (> 1 doubling dilution), and 43 non-responders (one subject did not have the follow-up PC_{20} due to technical problems).

Table 3 demonstrates the biomarkers and characteristics predicting the FEV_1 response. The predictors with strong correlation for ICS response were maximum albuterol reversibility with a correlation of r=0.83 (p<0.001). The initial four albuterol actuations were tightly linked to the maximal response, r=0.93. The FEV_1/FVC ratio was also significantly correlated to the ICS FEV_1 response, r= −0.75 (p<0.001) as was the baseline FEV_1 % predicted, r=−0.71 (p<0.001).

To separate the effect of a low baseline FEV_1 and maximum albuterol reversibility on FEV_1 response to an ICS, both predictors were included simultaneously in a regression model. The baseline FEV_1 was no longer a significant predictor, p=0.21, while baseline maximum reversibility remained a significant predictor, p<0.001.

The biomarkers and characteristics predicting BHR (PC_{20}) (Table 3) showed a poor correlation coefficient for sputum eosinophils of r=0.04, p=0.59. Asthma duration was in the opposite direction of our initial study, in that we found a longer duration of asthma predicted a greater change in PC_{20} (r=0.23, p=0.008). No biomarker or characteristic approached a correlation coefficient of ≥ ± 0.6.

To determine if prior use of either an ICS or systemic corticosteroid influenced the 6-week ICS response, a comparison between no past use (n=19) and past use (n=52) was performed.

For the percent change in FEV_1, the responses were 4.9 ± 16.2% and 10.9 ± 16.4%, respectively (p=0.18). For PC_{20} (log 2 scale) the responses were 0.53 ± 2.0 and 0.57 ± 1.5, respectively (p=0.94).

Sixteen-week double-blind trial

Stratification by FEV_1—The characteristics that describe the responders and non-responders at the start of the 16-week double blind trial are shown in Table 4. Induced sputum cell differential of responders and non-responders to ICS at the start of the long term trial is shown in Figure 3. There were no significant differences in cell differential between groups. There was a trend to increased percentage of eosinophils in the responder group.

Asthma control measured by the "mini" ACQ and stratified by FEV_1 response demonstrated the following (Figure 4, Table 5). For subjects who were non-responders to ICS during the 6-week trial, it did not matter whether they were maintained on ICS (ACQ, 0.80 ± 0.13) or switched to a placebo (0.81 ± 0.13) for the 16 week trial. The ACQ was not different over the next 16 weeks, p=0.99. Conversely, for the subjects who were ICS responders short term, those maintained on ICS maintained their asthma control (0.74 ± 0.12) while those placed on a placebo had worse asthma control (1.23 ± 0.13), p=0.007.

Secondary outcomes are shown in Table 5. Similar to the ACQ results, these secondary outcomes demonstrate that for the non-responders to ICS in the short term, similar results were obtained independent of being maintained on the ICS for the next four months. However, if an ICS response was demonstrated in the short term, maintaining good overall asthma stability depended on the maintenance of ICS.

Retrospective Stratification by PC_{20}—For the ICS non-responders, with regard to PC_{20} stratification, the ACQ was similar regardless if maintained on ICS or not 0.84 ± 0.12 vs 0.91 ± 0.13, respectively (p=0.65). The secondary outcomes for the non-responders were also similar and not significantly different. For the ICS responders, the ACQ was significantly better on ICS (0.68 ± 0.14) compared to placebo (1.16 ± 0.16), p=0.02. The secondary outcomes also were improved with ICS maintenance.

DISCUSSION

This Asthma Clinical Research Network protocol prospectively evaluated biomarkers and characteristics associated with ICS response and additionally, determined whether a short term response or lack of response to ICS predicted longer term asthma control. With regard to biomarkers and characteristics as predictors of ICS response, only the response to a short acting β_2-agonist (albuterol), low percentage 0.6) predicted FEV_1, and FEV_1/FVC ratio had a strong ($r \geq \pm 0.6$) correlation with response. Of potential importance was the observation that a short term non-response to ICS, 6 weeks with ≤ 5% FEV_1 improvement, indicated that these individuals may not need ICS in their treatment program. That is, whether they were maintained on or taken off ICS, asthma control and other secondary outcomes of response were maintained and similar. It is important to note that of the 33 poor short term ICS responders, 17 were maintained on ICS long term and 3 of these improved their FEV_1 to the responder range after four additional months on ICS. The long term ICS improvement in FEV_1 for these three subjects (16, 14.5, and 12.3%) did not necessarily coincide with the baseline maximal β_2-agonist reversibility (21.6, 3.0, and 11.7%, respectively). For the subjects with a short-term ICS response in FEV_1, defined as improvement > 5%, who were subsequently taken off ICS, their asthma control worsened compared to subjects maintained on ICS (p=0.007). Secondary response outcomes had similar findings.

Although the prior Asthma Clinical Research Network study retrospectively demonstrated that albuterol response, FEV_1/FVC, FeNO, sputum eosinophils, and shorter duration of asthma diagnosis predicted ICS response as to FEV_1 or bronchial hyperresponsiveness (7), the present prospective study only showed the albuterol response, % predicted FEV_1, and FEV_1/FVC as strong predictive biomarkers. The inclusion and exclusion criteria were similar between the studies as well as the baseline lung function and bronchial hyperresponsiveness. For the present study compared to the prior study: the baseline FEV_1 was 73 vs 74% predicted and PC_{20} 0.75 vs 0.52 mg/ml, respectively. However, the biomarkers appeared different between the present study and the prior report. The FeNO was slightly lower in the present study, 13 vs 16 ppb, respectively. The present study had a higher percentage of subjects with an asthma diagnosis greater than 15 years, 71 vs 64%, and sputum eosinophils, 1.5 vs 1.0%, respectively. A similar β_2-agonist response was seen between studies, 21 vs 20%. Thus, besides the important difference between prospective and retrospective study analyses, some differences in baseline biomarkers could also have added to the differing study results.

Other investigators have suggested that FeNO and sputum eosinophils are markers of corticosteroid response. Little and colleagues (14) reported that elevated levels of FeNO and sputum eosinophils before treatment were predictors of improvement in FEV_1 with a course of oral corticosteroids. Smith and colleagues reported in 52 patients presenting with undiagnosed respiratory symptoms (27 asthmatic diagnoses) that the FeNO tertile of > 47 ppb predicted the greatest ICS response for all endpoints that they measured (15). For the 27 asthmatic subjects the FeNO >47 ppb resulted in a 14.8 ± 6.4% increase in FEV_1 after four weeks of ICS (fluticasone 500 mcg/d) therapy. In subjects with an FeNO 15-47 ppb, improvement in FEV_1 was only 7.3 ± 4.7% and if < 15 ppb, the improvement was 2.2 ± 4.9%. Our study, using different methodology for FeNO measurement, did not demonstrate a significant correlation between FeNO and ICS improvement in FEV_1. However, as with most reported studies, we had very few individuals with FeNO > 47 ppb. With respect to sputum eosinophils, Pavord and colleagues (16) demonstrated a significant positive correlation between sputum eosinophils and the improvement in PC_{20} with ICS treatment. Bacci and colleagues also demonstrated that improvement with ICS occurred in subjects with eosinophils > 3% for FEV_1, BHR, and symptoms (17). However, long term asthma control was not determined in either study. We also found a significant correlation between sputum eosinophils and FEV_1 improvement with ICS ($p=0.04$), but the correlation was weak $r=0.17$. Additionally, at the present time, induced sputum is not a practical clinical test (18).

Szefler and colleagues in children 6-17 years of age defined response to an ICS, fluticasone propionate, as an improvement of > 7.5% (19). Only 40% of these asthmatic subjects were responders to the ICS. Those that did respond had greater allergic inflammation (increased IgE, circulatory eosinophils, serum eosinophils cationic protein), increased FeNO, lower lung function, and decreased PC_{20}. We also found the lower FEV_1 relationship to exist in adults. Those subjects who were responders to ICS over the six week trial had a lower starting FEV_1 (68% predicted) compared to the non-responders 77% predicted. Thus, airway caliber may play a role indicating ICS responsiveness to some extent, but not totally since when low FEV_1 was combined with maximum albuterol reversibility in a regression model, the low FEV_1 was no longer a predictor of ICS response.

Deykin and colleagues demonstrated that the change in the percentage of induced sputum eosinophils during the first two weeks after ICS cessation was a useful predictor of subsequent deterioration of asthma control (20). Neither FeNO nor methacholine PC_{20} were robust for being able to predict stability or deterioration upon ICS withdrawal. Of interest, it was estimated that 48% of subjects with mild-to-moderate asthma could discontinue ICS therapy without an increased risk of asthma deterioration over a period of at least 14 weeks. Either the prior ICS eliminated the inflammatory process or these subjects were poor responders to begin

with. When prospective monitoring of either FeNO (21) or sputum eosinophils (22) have been used as reference points to guide ICS dosing strategies, both have been found to be superior to standard care in maintaining control while minimizing ICS dosing burden over time. However, these trials answered different questions than posed by the ACRN study.

Since it appears that predictive biomarkers and characteristics can give varying results, our observation suggests an intriguing possibility that the use of a simple short term ICS trial (six weeks) based upon FEV_1 change appears to be a good indicator of longer term asthma control in our study population. Of the short-term non-responders to ICS, it did not matter whether they were maintained on or removed from this medication with regard to their long-term asthma control and other secondary outcome measures. Conversely, for short term responders, long term asthma control and secondary outcome measures were maintained with the continued use of ICS compared to removing this agent from the therapeutic regimen. Although the ICS induced change in PC_{20} to methacholine had some predictive value, these results were not as strong as for FEV_1. Additionally, BHR testing is not as practical for office practice use as is spirometry.

The duration of both the short term (six week) and long term (four month) trials can be critiqued for their relatively short time intervals. We elected a 6-week short term interval as our prior study (7) demonstrated that if a subject did not respond with regard to FEV_1 or PC_{20} in six weeks, progressive increases in ICS dosing over the next 15 weeks did not produce a further change in the results. Furthermore, Szefler and colleagues analyzed eight randomized, double-blind, placebo controlled clinical trials of at least 8-weeks duration and determined that the best observed effect with ICS occurred within three to four weeks for peak expiratory flow, asthma symptoms, supplemental albuterol use and FEV_1 (23). As to long term asthma control, no study has addressed the issue of the length of time ICS are needed to be used to determine maximal benefit. However, for good to total asthma control, Bateman and colleagues demonstrated that even when the dose of fluticasone-salmeterol combination was increased to 500/50 mcg for one year and a two-week oral corticosteroid burst was added, approximately 30% of asthmatic subjects still were not well controlled depending on severity at enrollment (8).

In summary, the short term response to ICS leading to FEV_1 improvement appears to predict long term asthma control. With this relatively simple office procedure, spirometry, a determination of response can guide decision making in those patients who are ICS naïve or have been off ICS for a period of time, as to the continued use of ICS or elimination of it from the therapeutic regimen. However, it must be stressed that these results need to be confirmed in larger, longer term studies. If these follow-up studies, indeed, validate the results of our study, different therapeutic strategies would need to be established for the ICS non-responders.

Clinical Implications: The decision to use long term inhaled steroids could be based on a short term trial. Different therapeutic strategies would need to be established for non-responders.

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Abbreviations

ACQ	Asthma Control Questionnaire
ACRN	Asthma Clinical Research Network
BD	Bronchodilator
BHR	bronchial hyperresponsiveness
FeNO	Fraction of exhaled nitric oxide
FEV_1	Forced expiratory volume in one second
GOAL	Gaining Optimal Asthma Control
HFA-BDP	hydrofloroalkaline-beclomethasone proprionate
ICS	Inhaled corticosteroids
Mcg	micrograms
NHLBI	National heart, Lung and Blood Institute
PC_{20}	Provocative concentration of methacholine producing a 20% fall in FEV_1
PEF	peak expiratory flow

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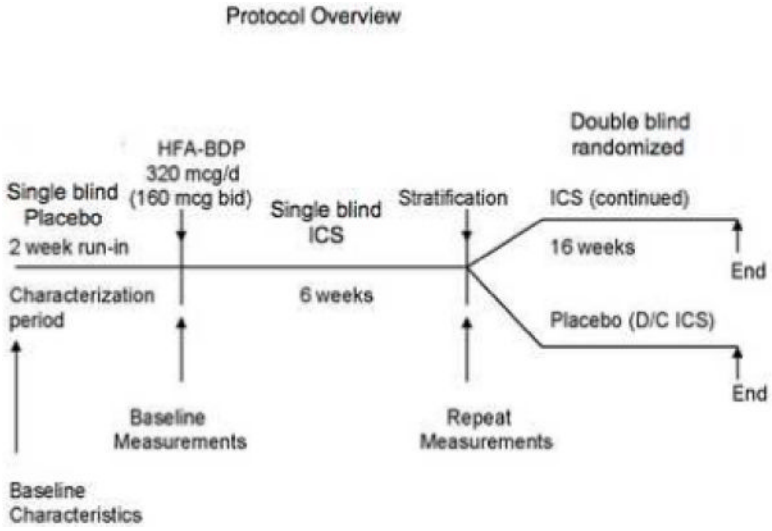

Figure 1.

Demonstrates the protocol time line with the different interventions. Stratification is based on the 6-week inhaled corticosteroid (ICS) response: poor, intermediate, and good. Baseline and repeat measurements included the biomarkers of β_2-agonist response, FeNO, and induced sputum eosinophils. Duration of asthma diagnosis was initially obtained. The "mini" Asthma Control Questionnaire was measured prior to the 16-week trial and once every month during the 16 weeks.

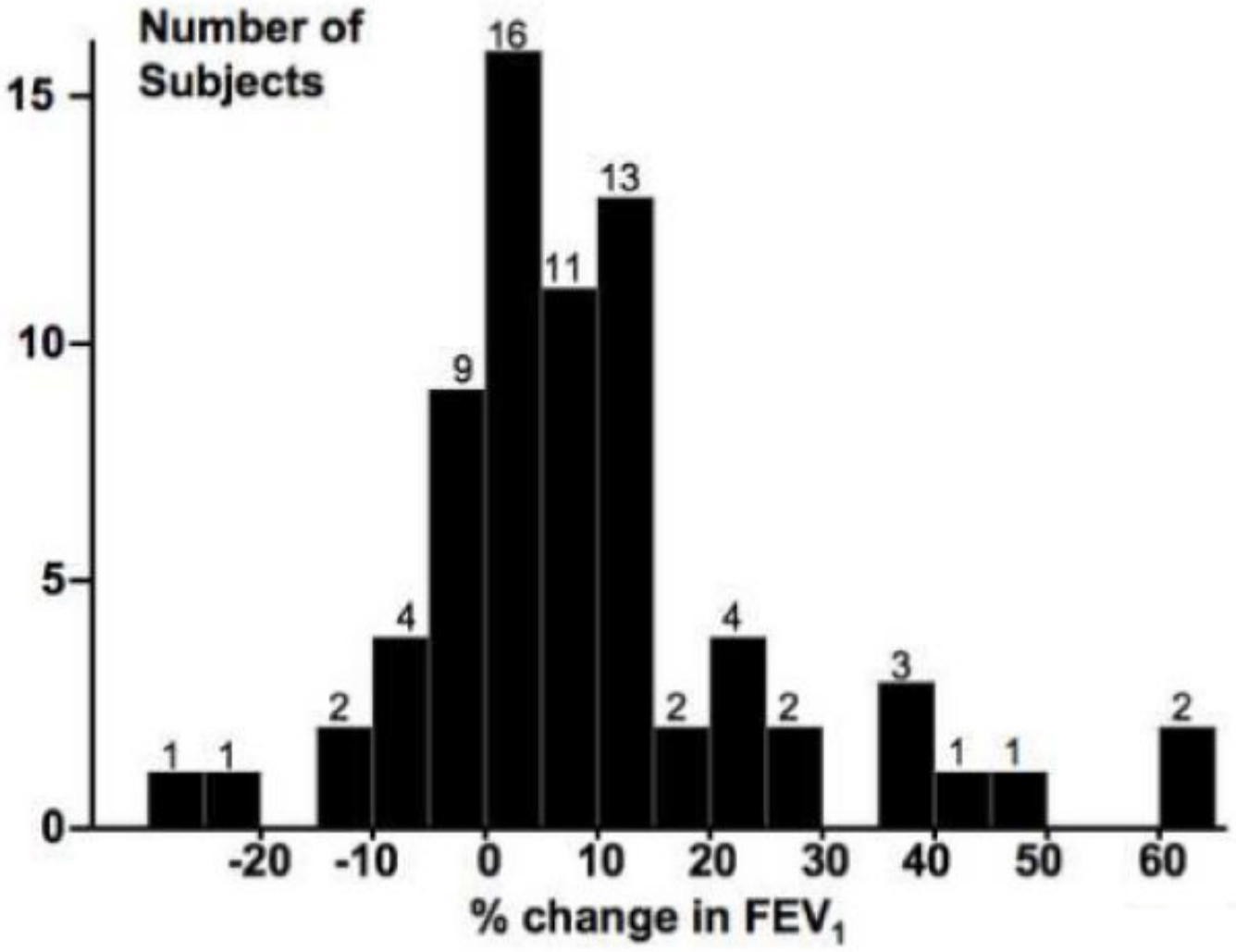

Figure 2.
The FEV_1 distribution response to inhaled corticosteroid over the short term 6-week trial. Bars represent 5% increments in FEV_1 response.

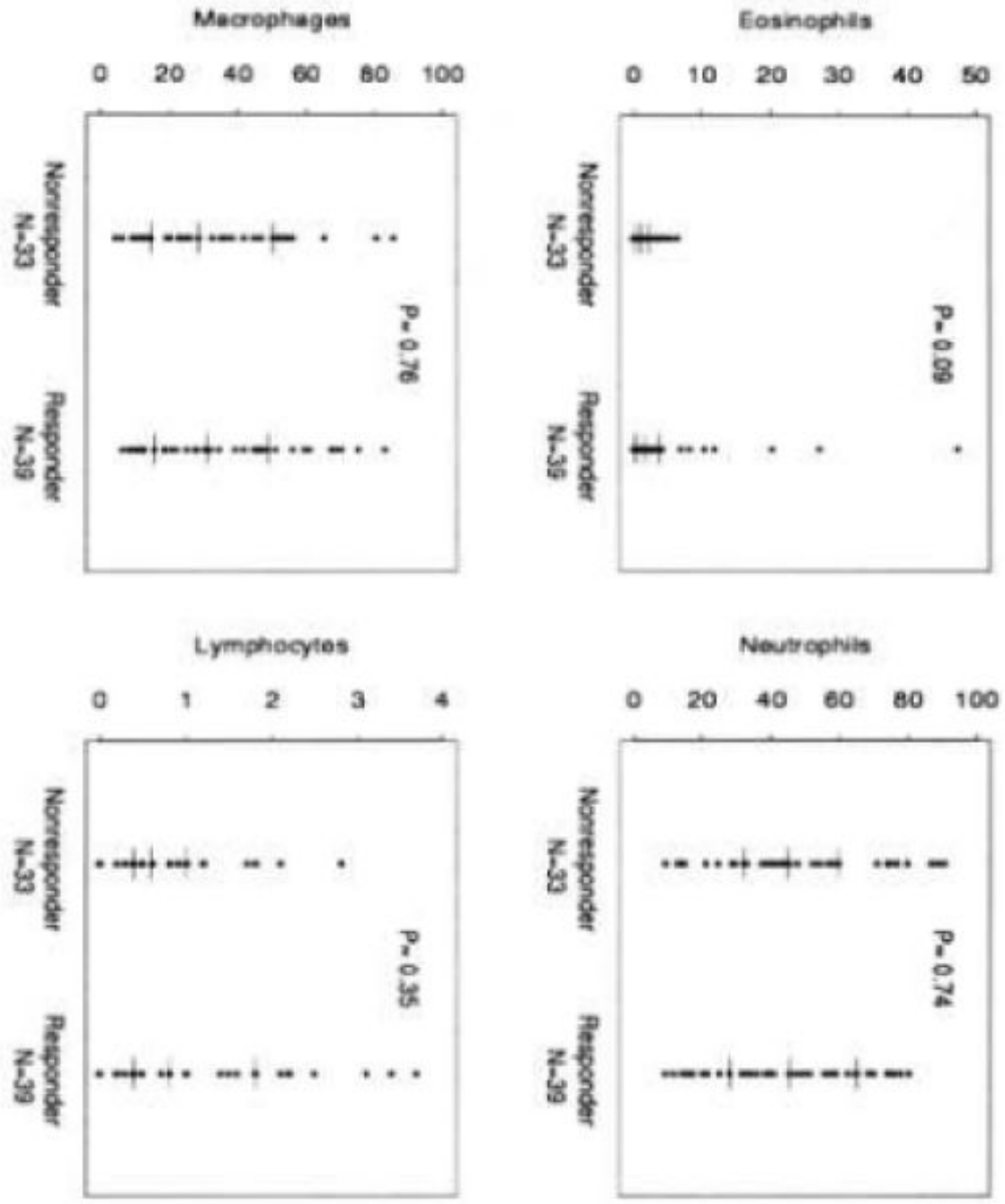

Figure 3.
Induced sputum characteristics stratified by inhaled corticosteroid response (post 6-week trial, prior to long term trial). Horizontal lines represent 25th, 50th, and 75th percentile.

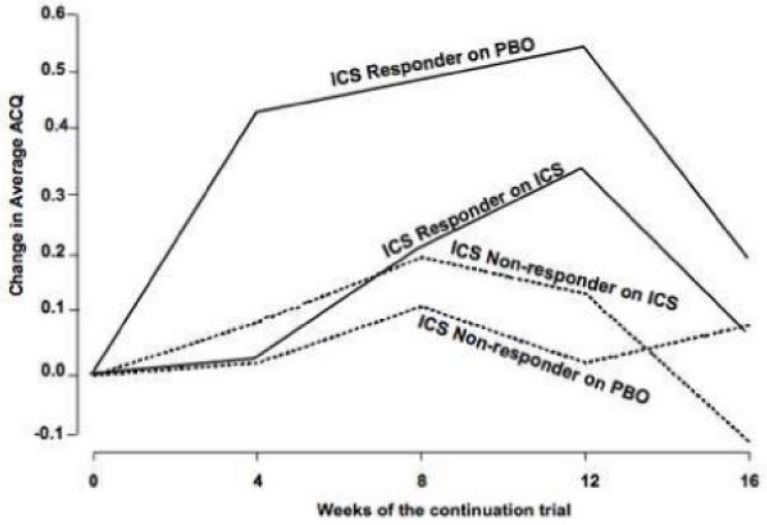

Figure 4.

Asthma control as measured by the asthma control questionnaire (ACQ) over the 16-week inhaled corticosteroid (ICS) or placebo (PBO) continuation trial. The groups are categorized based on the FEV_1 results of the prior 6-week ICS trial: Non-responders ≤ 5% improvement to ICS; Responders > 5% improvement on ICS. Only significant within group difference occurred between PBO and ICS responder groups, p=0.007. A lower ACQ score equates to better asthma control. PBO = placebo; ICS = inhaled corticosteroid.

Table 1

Baseline descriptive characteristics for 6-week trial (n=72)

Male/Female	32/40
Minority n (%)	32 (44.4)
Duration of asthma n (%)	
Less than 1 year	1 (1.4)
1 – 4 years	0 (0.0)
5 – 9 years	12 (16.7)
10 – 14 years	10 (13.9)
15 years or more	49 (68.1)
Oral corticosteroid use n (%)	41 (56.9)
Mean time since use (range) months	33 (1-216)
ICS use n (%)	44 (61)
Mean time since use (range) months	27.4 (1.2-120)
	Mean ± SD
Age	33.15 ± 9.14
FEV_1 (liters)	2.64 ± 0.65
FEV_1 % predicted	72.63 ± 10.64
Maximum Reversibility %	20.98 ± 16.85
Average ACQ score	1.00 ± 0.68
Nitric Oxide (ppb)[+]	13.9, 9.5,25.8
Sputum Eosinophils (%)[+]	1.50, 0.40,3.30
Methacholine PC20 (mg/ml)[++] (n=69)	0.75, 1.22
IgE (IU) [++]	206.7 1.38

[+]Median and 1st and 3rd quartiles are reported.

[++]Geometric mean and coefficient of variation are reported.

Table 2

Baseline FEV1 (% predicted) and FEV_1/FVC for ICS responders and non-responders

	Responders n=39	Non-responders n=33	P - value
	$\bar{x}$ ± SD	$\bar{x}$ ± SD	
FEV_1 % predicted	68.5 ± 10.4	77.5 ± 8.8	<0.001
FEV_1/FVC	0.65 ± 0.1	0.76 ± 0.1	<0.001

	Median (IQR)	Median (IQR)	
Sputum eosinophils - %	1.7 (0.4, 3.8)	1.1 (0.2, 2.4)	P = 0.09
FeNO - ppb	15.4 (10.1, 26.1)	13.0 (9.4, 20.7)	P = 0.68

Table 3

Biomarkers and characteristics predicting ICS response.

Baseline Predictors	FEV_1 Response			PC_{20} Response		
	n	Coefficient	P-value	n	Coefficient	P-value
max rev	72	0.83	0.001P	71	0.16	0.13P
median FeNO	72	0.04	0.63K	71	0.15	0.08K
eos	72	0.17	0.04K	70	0.04	0.59K
duration of asthma years (ordinal)	72	0.20	0.04K	71	0.23	0.008K
gender	72	0.08	0.46K	71	−0.13	0.21K
minority	72	−0.04	0.71K	71	−0.04	0.69K
age	72	0.02	0.86P	71	−0.04	0.68P
height	72	−0.01	0.95P	71	0.10	0.44P
weight	72	−0.04	0.71P	71	−0.29	0.52P
FEV_1/FVC	72	−0.75	<0.001P	71	−0.09	0.41P
FEV_1	72	−0.44	<0.001P	71	0.17	0.28P
FEV_1 % pred	72	−0.71	<0.001P	71	0.13	0.33P
am PEFx2wks	72	−0.18	0.06P	71	0.24	0.06P
pm PEFx2wks	72	−0.12	0.19P	71	0.25	0.06P
symtomsx2wks	72	0.13	0.13K	71	0.10	0.22K
rescue albuterolx2wks	71	0.26	0.006K	70	0.05	0.56K
pc20	69	−0.44	0.005P	71	−0.43	0.02P
ACQ	72	0.20	0.06P	71	0.09	0.44P
IgE	67	0.16	0.15P	66	−0.08	0.55P
positive skin test	69	0.20	0.06K	68	0.14	0.18K

P=Pearson Correlation Coefficients reported for normally distributed predictors.

K=Kendall's Tau-b Correlation Coefficients reported for ordinal and skewed predictors.

FeNO=Fraction exhaled nitric oxide.

eos=eosinophils from induced sputum.

max rev=maximum reversibility.

am PEFx2wks=morning peak expiratory flow rates for a 2-week period.

pm PEFx2wks=evening peak expiratory flow rates for a 2-week period.

ACQ=Asthma Control Questionnaire.

Table 4

Baseline descriptive characteristics at the start of the 16-week trial

Baseline Characteristic	Nonresponder (≤ 5%)		Responder (> 5%)	
	Placebo (n=16)	ICS (n=17)	Placebo (n=19)	ICS (n=20)
	N (%)	N (%)	N (%)	N (%)
Male, n (%)	9 (56.3)	8 (47.1)	9 (47.4)	6 (30.0)
Minority, n (%)	5 (31.3)	11 (64.7)	5 (26.3)	11 (55.0)
Allergy, n (%)	14 (87.5)	15 (93.8)	19 (100.0)	17 (94.4)
Duration ≥ 10 years, n (%)	11 (68.8)	15 (88.2)	15 (78.9)	18 (90.0)

Baseline Characteristic	Nonresponder (≤ 5%)				Responder (> 5%)			
	Placebo		ICS		Placebo		ICS	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
FEV_1 (liters) before ICS	2.86	0.18	2.87	0.20	2.47	0.09	2.43	0.13
FEV_1 (liters) after 6-week ICS	2.80	0.17	2.74	0.17	3.03	0.11	2.76	0.12
FEV_1 % predicted before ICS	77.25	2.43	77.76	1.98	66.26	2.37	70.60	2.29
FEV_1 % predicted after 6-week ICS	75.56	2.60	74.82	2.13	80.53	1.52	80.60	1.84
ACQ before ICS	0.77	0.16	0.94	0.18	1.36	0.13	0.89	0.15
ACQ after 6-week ICS	0.80	0.18	0.72	0.15	0.82	0.15	0.45	0.14

ICS=Inhaled corticosteroid ACQ=Asthma Control Questionnaire

Table 5

Four month ICS outcome measures; longitudinal analysis

	Non-responders ($FEV_1 \leq 5\%$)			Responders ($FEV_1 > 5\%$)			
Asthma Control Measure	**Placebo adjusted* mean(se)**	**ICS adjusted* mean(se)**	**P-value**	**Placebo adjusted* mean(se)**	**ICS adjusted* mean(se)**	**P-value+**	**Trend Test P-value+**
Average ACQ Score	0.81(0.13)	0.80(0.13)	0.99	1.23(0.13)	0.74(0.12)	0.007	0.016
Average AM Peak Flow	415.0(7.0)	427.9(6.8)	0.18	404.9(6.7)	425.1(6.2)	0.02	0.009
Average Rescue Puffs/d	1.07(0.18)	0.87(0.18)	0.42	1.38(0.18)	0.72(0.17)	0.009	0.008
FEV_1 % predicted	76.29(1.28)	78.45(1.26)	0.23	70.62(1.26)	78.53(1.15)	<0.001	<0.001
Percent Symptom Free Days	55.4(5.6)	63.4(5.5)	0.31	48.8(5.5)	60.1(5.1)	0.14	0.078
Percent Symptom Free Nights	62.4(4.9)	72.4(4.8)	0.15	56.8(4.9)	70.8(4.5)	0.04	0.014
Exacerbations-number	0	1	0.33	4	0	0.03	0.065

*Adjusted for value prior to randomization and visit over the 4-month inhaled corticosteroid/placebo trial.

+P-values from stratified repeated measures analysis of covariance models except for exacerbations which were compared using the log-rank test for time-to-event. Within group p-value compares placebo to ICS. The trend test p-value tests whether a linear trend exists between the placebo – ICS difference in the non-responders and the placebo – ICS difference in the responders.