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Comparison of Physician-, Biomarker-, and Symptom-Based Strategies for Adjustment of Inhaled Corticosteroid Therapy in Adults With Asthma:

The BASALT Randomized Controlled Trial

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Abstract

Context—No consensus exists for adjusting inhaled corticosteroid therapy in patients with asthma. Approaches include adjustment at outpatient visits guided by physician assessment of asthma control (symptoms, rescue therapy, pulmonary function), based on exhaled nitric oxide, or on a day-to-day basis guided by symptoms.

Objective—To determine if adjustment of inhaled corticosteroid therapy based on exhaled nitric oxide or day-to-day symptoms is superior to guideline-informed, physician assessment–based adjustment in preventing treatment failure in adults with mild to moderate asthma.

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Online-Only Material: eSupplement, 2 eTables, the eFigure, and the Author Video Interview are available at http://www.jama.com.

Design, Setting, and Participants—A randomized, parallel, 3-group, placebo-controlled, multiply-blinded trial of 342 adults with mild to moderate asthma controlled by low-dose inhaled corticosteroid therapy (n=114 assigned to physician assessment–based adjustment [101 completed], n=115 to biomarker-based [exhaled nitric oxide] adjustment [92 completed], and n=113 to symptom-based adjustment [97 completed]), the Best Adjustment Strategy for Asthma in the Long Term (BASALT) trial was conducted by the Asthma Clinical Research Network at 10 academic medical centers in the United States for 9 months between June 2007 and July 2010.

Interventions—For physician assessment–based adjustment and biomarker-based (exhaled nitric oxide) adjustment, the dose of inhaled corticosteroids was adjusted every 6 weeks; for symptom-based adjustment, inhaled corticosteroids were taken with each albuterol rescue use.

Main Outcome Measure—The primary outcome was time to treatment failure.

Results—There were no significant differences in time to treatment failure. The 9-month Kaplan-Meier failure rates were 22% (97.5% CI, 14%-33%; 24 events) for physician assessment–based adjustment, 20% (97.5% CI, 13%-30%; 21 events) for biomarker-based adjustment, and 15% (97.5% CI, 9%-25%; 16 events) for symptom-based adjustment. The hazard ratio for physician assessment–based adjustment vs biomarker-based adjustment was 1.2 (97.5% CI, 0.6-2.3). The hazard ratio for physician assessment–based adjustment vs symptom-based adjustment was 1.6 (97.5% CI, 0.8-3.3).

Conclusion—Among adults with mild to moderate persistent asthma controlled with low-dose inhaled corticosteroid therapy, the use of either biomarker-based or symptom-based adjustment of inhaled corticosteroids was not superior to physician assessment–based adjustment of inhaled corticosteroids in time to treatment failure.

Trial Registration—clinicaltrials.gov Identifier: NCT00495157

Asthma is managed by consensus guidelines.[1,2] Disease activity varies daily, seasonally, and episodically, presumably related to airway inflammation.[3] Accordingly, asthma management requires periodic dose adjustments of controller medications, particularly inhaled corticosteroids. Adjustments have been based on (1) physician assessment of symptoms, activity limitation, rescue albuterol use, lung function, and exacerbations at usual office or clinic visits,[1] (2) a biomarker of disease activity (eg, exhaled nitric oxide, sputum eosinophils, methacholine responsiveness),[4-10] or (3) the occurrence of symptoms on a day-to-day basis.[11-13]

We hypothesized that adjustment of inhaled corticosteroids based on symptoms or exhaled nitric oxide would be superior to adjustment based on physician assessment. Our purpose was to ascertain whether symptom-based adjustment (SBA) of inhaled corticosteroids might be a simple and effective strategy for managing asthma therapy in a population of patients with asthma commonly seen in primary care settings, and to ascertain if biomarker-based adjustment (BBA) was superior to physician assessment–based adjustment (PABA).

METHODS

The Best Adjustment Strategy for Asthma in the Long Term (BASALT) randomized trial included 342 participants with mild to moderate persistent asthma; these individuals were recruited cooperatively with a concurrent Asthma Clinical Research Network (ACRN) trial[14] (Figure 1). The ACRN data and safety monitoring board and clinical center institutional review boards approved the protocol and consent form; all participants signed a written consent form. Race was self-reported as white, black, or other, and ethnicity as Latino or non-Latino, and recorded to assess representativeness in accordance with National Heart, Lung, and Blood Institute guidelines. All participants had a physician diagnosis of

asthma, and either reversible airflow limitation (≥12% improvement in forced expiratory volume in the first second of expiration [FEV_1] after 360 μg of albuterol), or airway hyperresponsiveness (provocative concentration of methacholine [<8 mg/mL] causing a 20% drop in FEV_1).

We evaluated these approaches to dose adjustment of inhaled corticosteroids in a 3-group trial during 9 months in adults with mild to moderate asthma that was well controlled with low-dose inhaled corticosteroids. The dose of inhaled corticosteroids was adjusted by (1) a strategy based on National Heart, Lung, and Blood Institute guidelines (PABA group), (2) measurement of exhaled nitric oxide (BBA group), or (3) occurrence of symptoms prompting rescue use of albuterol (SBA group). In the first 2 strategy groups, dose adjustments of inhaled corticosteroids were made at the time of clinic visits (every 6 weeks); in the third group, dose adjustment of inhaled corticosteroids was performed by matching inhaled steroid use on a puff-per-puff basis with as-needed albuterol use.

We selected these strategy groups because (1) PABA therapy represents standard care in the United States, (2) BBA in adults using exhaled nitric oxide may achieve good asthma control with reduced total use of inhaled corticosteroids,[5] and (3) SBA produces outcomes equivalent to daily controller therapy in patients with mild asthma.[11,12] We sought to determine if SBA would be successful in patients with more severe asthma than in our previous study of patients with mild persistent asthma.[11]

Patients were treated with 2 puffs twice daily of beclomethasone HFA (40 μg/puff) during the run-in period, and if their asthma was acceptably controlled (a score of 0 or 1 on each of 3 questions on the Asthma Evaluation Questionnaire [eSupplement at http://www.jama.com] and predicted bronchodilator FEV_1 >70%), they were enrolled in the BASALT trial. This approach yielded a population of participants with well or partially controlled asthma, but excluded those with poorly controlled asthma. During the prerandomization period, patients were given 3 inhalers coded as *A*, *B*, and *C*. Inhaler A contained beclomethasone HFA (40 μg/puff) and inhalers B and C contained placebo. An albuterol inhaler was provided for use as needed for asthma symptoms. Participants were instructed to use 2 puffs twice daily from inhalers A and B, and to use 2 puffs from inhaler C each time they used 2 puffs of albuterol for symptom relief. All metered dose inhalers were equipped with a Doser device (Meditrack Products) to measure adherence during the trial. Patients who demonstrated at least 75% adherence were randomized to 1 of 3 adjustment strategies: PABA, BBA, or SBA.

Beclomethasone HFA was provided at a dosage of 2 puffs twice daily (40 μg/puff) before randomization, corresponding to level 3 treatment. Hence, inhaled corticosteroid therapy could be intensified or deintensified during the trial. Following randomization, beclomethasone HFA was contained only in inhaler A for PABA participants, only in inhaler B for BBA participants, and only in inhaler C for SBA participants. Thereafter, inhaler A was adjusted by an investigator according to guidelines closely resembling the National Heart, Lung, and Blood Institute National Asthma Expert Panel,[1] and inhaler B was adjusted according to exhaled nitric oxide measurements. Participants were instructed to use inhaler C only at the time of albuterol use. Subsequent visits occurred 2, 4, 6, 12, 18, 24, 30, and 36 weeks after randomization, at which times outcomes were measured (the BASALT Protocol appears at http://www.acrn.org/BASALT.html).

Our primary outcome was time to first treatment failure, a clinically important worsening of asthma (BOX).[11] Hospitalizations, urgent care visits, and other adverse events were recorded at the time of scheduled clinic visits. Spirometry, albuterol reversibility, methacholine responsiveness, sputum eosinophils, daytime and nighttime symptom and rescue β-agonist diaries, Asthma Control Questionnaire, Asthma Symptom Utility Index,

and Asthma Quality-of-Life Questionnaire were measured as in previous ACRN trials[11] as secondary outcomes. We analyzed the frequency of exacerbations (treatment failures requiring systemic corticosteroids, an unscheduled physician contact for asthma, or severe symptoms linked to lung function decline[11]), and quantified use of inhaled corticosteroids. The BASALT protocol at http://www.acrn.org/BASALT.html details the frequency and timing of each outcome measure.

The BASALT trial was a parallel, 3-group trial with 2 primary comparisons: PABA vs SBA and PABA vs BBA. Based on proposed enrollment, we had 87% power to detect a 60% reduction in treatment failure rate (30% vs 12%), as previously observed,[5] for an overall α level of .05 (.025 for each primary comparison), and a postrandomization dropout rate of 15%. The comparison between SBA and BBA was exploratory.

To evaluate time to first treatment failure, Kaplan-Meier survival plots and logrank tests were generated. A Cox proportional hazards regression model compared time to first treatment failure with adjustment for covariates of center and baseline FEV_1. To accommodate multiple treatment failures, a repeated-measures proportional hazards regression model was fit to time to treatment failure, with adjustment for center and baseline FEV_1. Methods for secondary analyses are described in the BASALT protocol.

All analyses followed intention-to-treat principles and incorporated all available data. The statistical models and analyses for the primary and secondary outcomes assumed missing data were missing at random. Because 2 primary comparisons were of interest, PABA vs BBA and PABA vs SBA, comparisons were evaluated for statistical significance at the .025 level, as was the secondary comparison of BBA vs SBA, for both primary and secondary outcomes. Statistical tests were 2-sided and all statistical analyses were performed using SAS version 9.3 (SAS Institute Inc).

RESULTS

Randomization allocated 114 to PABA, 115 to BBA, and 113 to SBA, with no important differences among the groups at baseline. Participant characteristics were consistent with mild to moderate persistent asthma: mean FEV_1 was 86% predicted, provocative concentration of methacholine (<3 mg/mL) causing a 20% drop in FEV_1, and mean Asthma Control Questionnaire score was 0.75 (Table 1). Details regarding dosing adjustment of inhaled corticosteroids appear in Table 2. The dropout rate during the trial did not differ significantly among groups (20% for BBA vs 11% for PABA vs 14% for SBA). Median adherence in all groups exceeded 95%.

Time to treatment failure, our primary outcome, did not differ significantly among the 3 treatment strategies. The 9-month Kaplan-Meier failure rates were 22% (97.5% CI, 14% to 33%; 24 events) for PABA, 20% (97.5% CI, 13% to 30%; 21 events) for BBA, and 15% (97.5% CI, 9% to 25%; 16 events) for SBA. The hazard ratio (HR) for PABA vs BBA was 1.2 (97.5% CI, 0.6 to 2.3; log-rank P=.68); PABA vs SBA, 1.6 (97.5% CI, 0.8 to 3.3; P=.18); and BBA vs SBA, 1.4 (97.5% CI, 0.6 to 2.9; P = .35) (Figure 2). The 9-month Kaplan-Meier treatment failure rates resulted in average differences of 2 (range: −10 to 14) percentage points for PABA vs BBA and 7 (range: −5 to 19) percentage points for PABA vs SBA (ie, more events for PABA).

Treatment failure rates were not different among groups when multiple episodes of treatment failure were included (0.43 [97.5% CI, 0.23-0.64] events/person-year for PABA vs 0.27 [97.5% CI, 0.14-0.39] events/person-year for BBA and 0.25 [97.5% CI, 0.10-0.39] events/person-year for SBA; P=.21). The HR for PABA vs BBA was 1.5 (97.5% CI,

0.8-2.9); PABA vs SBA, 1.7 (97.5% CI, 0.9-3.3); and BBA vs SBA, 1.2 (97.5% CI, 0.6-2.3).

Mean monthly beclomethasone use was higher in both the PABA (1610 μg) and BBA (1617 μg) groups than in the SBA group (832 μg; *P*=.01 for both comparisons). The frequency distribution of prescribed inhaled corticosteroid doses did not differ between the PABA and BBA groups (*P* = .99; Figure 3). During the study, participants tended to require less inhaled corticosteroids, with approximately 40% of the participants exhibiting acceptable asthma control while taking no beclomethasone during 1 or more visits. The secondary outcomes appear in eTable 1 at http://www.jama.com.

Few days were lost from school or work in our trial (0.25 [97.5% CI, 0.03-0.47] days/person-year for PABA, 0.46 [97.5% CI, 0.08-0.84] days/person-year for BBA, and 0.11 [97.5% CI, 0-0.23] days/person-year for SBA). However, the odds ratio (OR) of missing days was greater for BBA vs either PABA (OR, 2.0 [97.5% CI, 1.1-3.8]; *P*=.01) or SBA (OR, 4.3 [97.5% CI, 1.9-9.6]; *P*<.001).

Asthma exacerbation (including multiple episodes) rates did not differ among the treatment groups (0.23 [97.5% CI, 0.10-0.37] events/person-year for PABA vs 0.21 [97.5% CI, 0.10-0.32] events/person-year for BBA and 0.12 [97.5% CI, 0.03-0.21] events/person-year for SBA) (PABA vs BBA, *P*=.89; PABA vs SBA, *P*=.11; and BBA vs SBA, *P*=.13). The HR was 1.1 (97.5% CI, 0.4-2.8) for PABA vs BBA; 2.0 (97.5% CI, 0.8-5.4) for PABA vs SBA; and 1.9 (97.5% CI, 0.7-4.9) for BBA vs SBA.

The mean proportion of treatment failures that progressed to exacerbations did not differ significantly among treatment groups (PABA: 0.58 [SD, 0.46]; BBA: 0.79 [SD, 0.41]; and SBA: 0.48 [SD, 0.47]; *P*=.13). The comparison between PABA and BBA yielded a pairwise *P* value of .08; PABA vs SBA, *P*=.65; and BBA vs SBA, *P*=.05.

Measures of lung function and asthma symptoms were not significantly different among the groups (Figure 4, eTable 1). Airway responsiveness worsened in the PABA group compared with the BBA group (*P*<.006; eTable 1), but did not differ when the SBA group was compared with the other 2 groups.

Exhaled nitric oxide and sputum eosinophils were not different in the 3 treatment groups at baseline. The increase in exhaled nitric oxide was significantly greater in the SBA group than in the BBA group (*P*=.007), but did not differ between the BBA and PABA groups or between the SBA and PABA groups (Figure 4). Serious adverse events were uncommon (eTable 2).

Predictors of time to treatment failure were race (*P*=.001) and albuterol reversibility (*P*=.004). Hispanic (OR, 3.6; 95% CI, 1.8-7.0) and black (OR, 2.1; 95% CI, 1.2-4.0) participants had significantly greater risk for first treatment failure than did non-Hispanic white participants (*P*<.02 for both comparisons). A multivariable model confirmed these same predictors for multiple treatment failures. Notably, baseline FEV_1, peak flow, symptoms, exhaled nitric oxide, and sputum eosinophils did not predict treatment failure.

There was a significant association of race and efficacy with the SBA and PABA groups (eFigure). Among Hispanic participants, treatment failure was better prevented in the PABA group than in the SBA group, which contrasted with non-Hispanic whites. The HR for treatment failure with PABA vs SBA among non-Hispanic whites was 4.50 (95% CI, 1.42-14.30) and among Hispanics it was 0.30 (95% CI, 0.04-1.80) (comparing HRs yielded *P*=.01).

We observed an interaction of season with treatment failure in the PABA participants, in whom treatment failure increased 4-fold during autumn, significantly more than in the BBA and SBA groups (P=.02; Figure 5).

COMMENT

The principal finding of this blinded, randomized controlled trial was that the rate of episodes of clinical worsening of asthma (ie, treatment failure) associated with instructing participants to take 2 puffs of low-dose beclomethasone every time they took 2 puffs of albuterol for relief of symptoms (SBA group) was not lower than the rate associated with adjusting the dose of inhaled corticosteroids based on physician assessment of symptoms, rescue use of albuterol, and pulmonary function at 6 week intervals (PABA group). Similarly, adjustment of the dose of inhaled corticosteroids based on measurement of exhaled nitric oxide at 6-week intervals (BBA group) was not associated with lower rates of treatment failure compared with PABA. Among the 18 secondary or exploratory outcomes, the outcomes of missed days from school or work and cumulative doses of inhaled corticosteroids were significantly lower in the SBA group compared with the PABA group.

Controller adjustment strategies differ in the features of asthma assessed and in the temporal coupling between changes in these features and adjustments in dose of inhaled corticosteroids. PABA management is a de facto standard of care. The weaknesses are its complexity and its loose temporal relationship between variations in asthma control and adjustment in dose of inhaled corticosteroids. The same is true of adjustments based on sputum eosinophils,[7,8] exhaled nitric oxide, or methacholine responsiveness,[9] which have had limited penetration into practice. Of available biomarkers, exhaled nitric oxide is the easiest to implement, but adjustment based on exhaled nitric oxide was no more effective than the other strategies.

Symptom-based adjustment strategies are appealing because they are simple to use and empower patients. Whether these features might improve adherence to therapy was not testable in this closely monitored trial. Requiring all participants to use 2 inhalers (A and B) twice daily and a third (inhaler C) with symptoms could easily have masked a benefit in quality of life from the smaller burden of care with the SBA approach.

Other studies have shown symptomdriven treatment with inhaled corticosteroids performing as well as daily treatments. In the Improving Asthma Control Trial (IMPACT),[11] participants with mild persistent asthma received daily inhaled corticosteroids, zafirlukast, or placebo, plus 10 days of high-dose inhaled corticosteroids triggered by a symptom-based action plan. Asthma outcomes, including treatment failure, did not differ by treatment. BASALT participants had significantly more severe asthma than IMPACT participants.[11] Despite treatment with daily beclomethasone during the BASALT run-in period (contrasted with only as-needed albuterol in IMPACT), mean values for FEV_1 (2.96 L [86%]) and AM peak expiratory flow (447 L/m) were significantly lower at randomization in BASALT (vs IMPACT: 3.19 L [89%] for FEV_1 and AM peak expiratory flow of 465 L/m) (BASALT vs IMPACT: P=.049 for AM peak expiratory flow; P<.001 for FEV_1).

The Beclomethasone plus Salbutamol Treatment (BEST)[12] study showed that as-needed combination therapy with beclomethasone and albuterol was superior to as-needed albuterol alone, and comparable with twice daily beclomethasone plus as-needed albuterol. BEST resembles BASALT in showing that as-needed combination therapy reduces cumulative dose of inhaled corticosteroids. In BEST participants whose asthma was comparable with BASALT, the dose of beclomethasone used was 250 μg/puff, which is 6 times the dose used in BASALT.

O'Byrne et al[13] showed that combination formoterol and budesonide for both maintenance and relief of symptoms resulted in better asthma control than scheduled treatment alone. The participants had more severe asthma, and received daily maintenance treatment with inhaled corticosteroids. For US practitioners, it should be noted that use of a single combination inhaler for both maintenance and rescue treatment does not align with current US Food and Drug Administration policy. The innovation of BASALT is to couple the use of reliever and controller treatments that are approved by the Food and Drug Administration for their respective indications in a symptomdriven adjustment strategy.

We observed a slight increase in exhaled nitric oxide in the SBA group (14 ppb vs 5 ppb in BBA; 10 ppb in PABA), which is not surprising because the dose of inhaled corticosteroids in the BBA group was adjusted by fraction of exhaled nitric oxide. Similar small elevations in exhaled nitric oxide have been observed in patients with asthma considered too mild to warrant daily controllers[17] and in patients whose asthma is in clinical remission.[18]

Symptom-based adjustment of inhaled corticosteroids in patients with mild to moderate asthma accomplishes temporal personalization of controller therapy and provides several advantages. Insofar as asthma triggers intensify airway inflammation (eg, allergens, viruses), the prompt increase in anti-inflammatory medication could offset the inflammogenic stimulus. Our observation that PABA participants had significantly more exacerbations during autumn, a period of increased viral infections and allergen exposure, while SBA participants did not, is consistent with this concept. That early intervention may prevent worsening of asthma to exacerbation is suggested by the finding that quadrupling the dose of inhaled corticosteroids at the onset of symptoms reduced the risk of requiring oral corticosteroids.[19]

Our findings provide reassurance that SBA of inhaled corticosteroids dose may be appropriate in most patients with mild to moderate asthma. Patients with asthma who poorly perceive their symptoms might be expected to have less favorable outcomes with SBA, but we could not directly assess this possibility. Moreover, patients who are poorly adherent to prescribed therapy would be expected to mimic our group of SBA participants, using their therapy only when symptoms dictate. There may be ethnic differences in the associations of adjustment strategies with study outcomes because the small number of Hispanic participants in our study did not have as robust a response to SBA relative to PABA (eFigure). This finding seems unlikely to have been a function of differential access to care or medication, but could reflect linguistic, sociocultural,[20,21] or ethnic-specific environmental or pharmacogenetic differences that affect responses to triggers.[22,23]

Several limitations of our study are worth noting. Our sample size was too small to determine the associations of ethnicity and race with responsiveness to adjustment strategy for most outcomes. It is possible that some nonsignificant outcome differences could achieve significance with a larger sample size. However, the point estimates on most of these outcomes favored SBA over BBA or PABA, so the likelihood of us having missed an important detrimental association is small. Furthermore, findings in well-controlled clinical trials may not translate directly to clinical practice.

Power calculations were performed based on the assumption of a certain treatment failure rate in our population of interest, and a percentage reduction that we deemed as clinically meaningful (60% treatment failure reduction from 30% in the PABA group to 12% in the BBA or SBA groups). These estimates were based on published literature. If we had observed this size of reduction but without statistical significance, our study would have been underpowered. However, we observed reductions in treatment failure rates of 9% (22% for PABA vs 20% for BBA) and 32% (22% for PABA vs 15% for SBA), indicating that the

treatment approaches were more similar in preventing treatment failure than anticipated. A very large study might be needed to demonstrate statistical significance for a difference in treatment failure rates of questionable clinical importance.

In summary, among adult participants with mild to moderate persistent asthma, neither the SBA nor the BBA strategy for inhaled corticosteroid therapy was superior to the standard PABA strategy for the outcome of treatment failure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Author Contributions: Dr Calhoun had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Calhoun and Ameredes contributed equally to the work.

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Box

Treatment Failure Criteria

Asthma exacerbation

unscheduled medical contact for increased asthma symptoms that results in use of oral corticosteroids, increased inhaled corticosteroids, or additional medications for asthma.

At-home measurements

any of the following 3 criteria, when not associated with the increased asthma symptoms, satisfies treatment failure criteria:

- Prebronchodilator $_{AM}$ peak expiratory flow (PEF) of less than 65% of baseline on 2 consecutive mornings, scheduled measurements.
- Postbronchodilator PEF of less than 80% of baseline despite 60 minutes of rescue β-agonist treatment. Postbronchodilator PEF may be taken at any time of day.
- An increase in albuterol use of more than 8 puffs per 24 hours over baseline use for a period of 48 hours, or more than 16 puffs per 24 hours for more than 48 hours.

In-clinic measurements

Prebronchodilator forced expiratory volume in the first second of expiration (FEV_1) values on 2 consecutive sets of spirometric determinations measured 24 to 72 hours apart that are less than 80% of the baseline prebronchodilator value (baseline value for adherence period: FEV_1 value at visit 3; baseline for randomization period: FEV_1 value at visit 4). All participants found to have an FEV_1 of less than 80% of baseline at any center visit but who are not considered to meet treatment failure or exacerbation criteria must be seen again within 72 hours to have FEV_1 measured.

Physician judgment for patient safety.

Patient dissatisfaction with asthma control achieved by study regimen.

Requirement for open-label inhaled corticosteroids or another (nonsystemic corticosteroid) new asthma medication (eg, montelukast) without the addition of systemic corticosteroids.

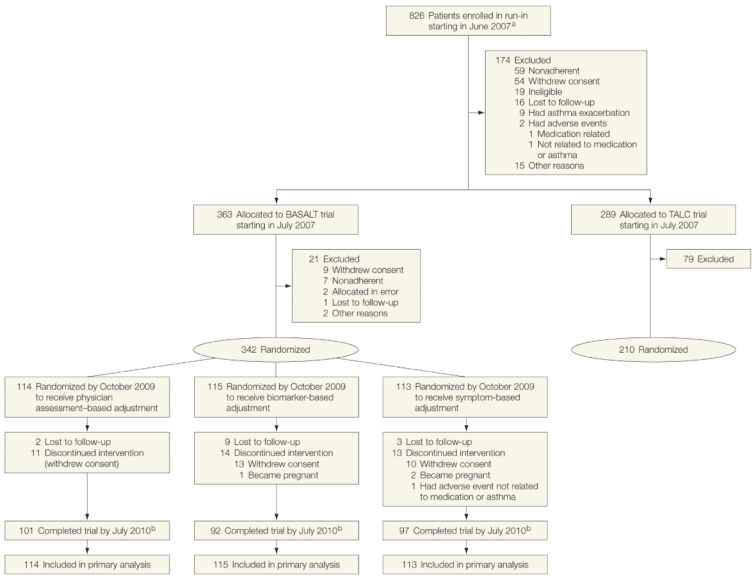

Figure 1.

Participant Allocation in BASALT and TALC Trials

Patients were allocated to the Best Adjustment Strategy for Asthma in the Long Term (BASALT) trial based on achievement of forced expiratory volume in the first second of expiration of greater than 70% during the run-in period and concomitant control of symptoms (score of 0 or 1 on each of 3 questions on the Asthma Evaluation Questionnaire; eSupplement at http://www.jama.com). Patients whose lung function was less than 70% of predicted or had quantitatively greater symptom burden were allocated to the Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC) trial, which was a concurrently recruited Asthma Clinical Research Network trial.[14]

[a]Details for those screened but ineligible were not collected.

[b]Dropouts were included as censored observations.

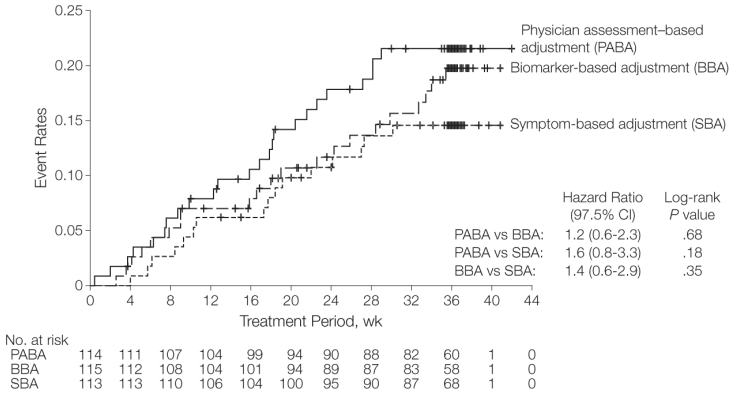

Figure 2.

Time to First Treatment Failure

No significant differences among the 3 treatment groups were seen. A confirmatory truncated analysis was performed with truncation at day 258 (week 37), beyond which less than 10% of the study population was still in follow-up. These results confirm the primary analysis with a pairwise *P* value for PABA vs BBA of .64; PABA vs SBA, *P*=.15; and BBA vs SBA, *P*=.33. The hazard ratios and 97.5% confidence intervals were identical to 1 decimal place. Short vertical bars on the curves indicate censored data.

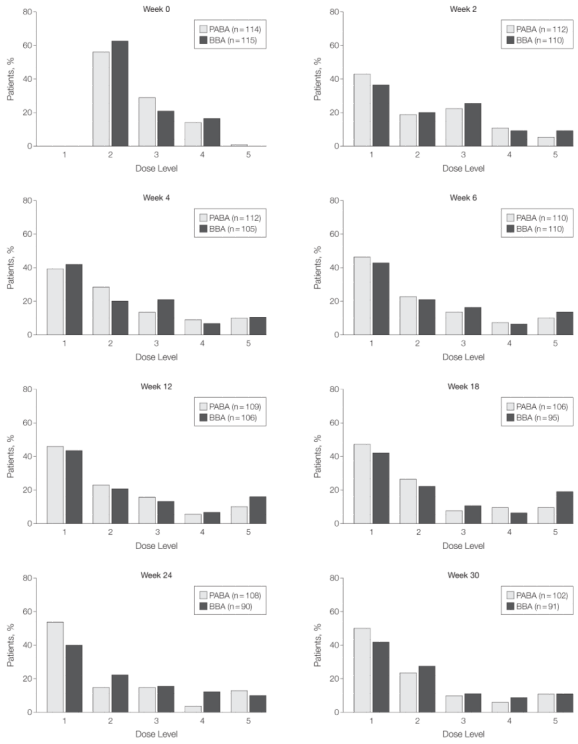

Figure 3.

Dose Level Distribution of Prescribed Inhaled Corticosteroids

No significant differences in dose distribution were observed between the biomarker-based adjustment (BBA) and the physician assessment–based adjustment (PABA) strategies. Because there was no regularly scheduled dose in the symptom-based adjustment group, equivalent dose distributions cannot be reliably calculated for participants randomized to this group. The corresponding dose and frequency for the dose levels appear in Table 2.

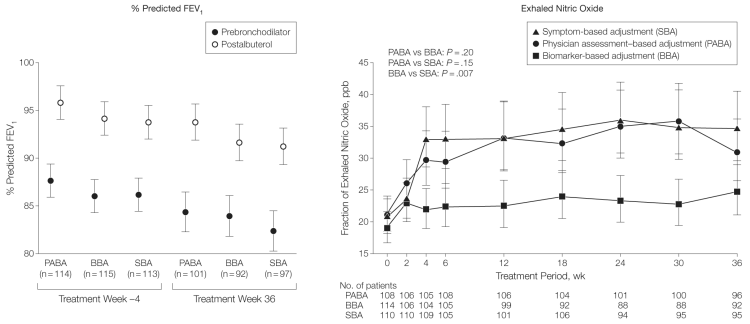

Figure 4.

Mixed-Model Treatment Means of Pulmonary Function and Exhaled Nitric Oxide

The data markers indicate geometric means and the error bars indicate 97.5% confidence intervals. FEV_1 indicates forced expiratory volume in the first second of expiration. No significant differences in prebronchodilator FEV_1, postbronchodilator FEV_1, or albuterol-induced reversibility were observed. The BBA group had very little change in exhaled nitric oxide over the course of the trial because dosing of inhaled corticosteroids was adjusted to control exhaled nitric oxide. The SBA group showed a small and statistically significant increase in exhaled nitric oxide over the course of the trial vs the BBA group (*P*=.007). Level of exhaled nitric oxide in the SBA group did not differ significantly from the PABA group (*P*=.15).

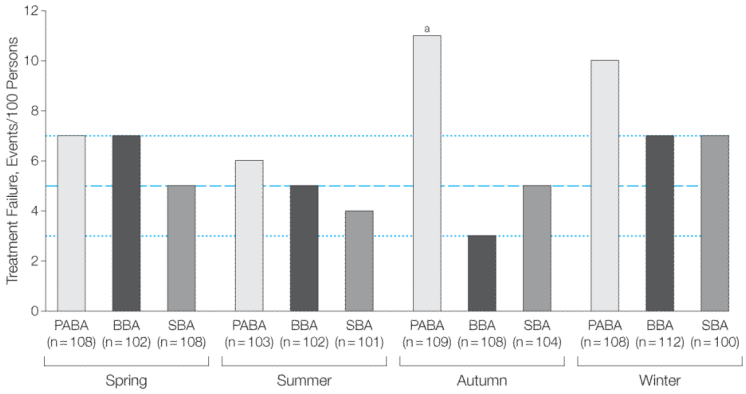

Figure 5.

Treatment Failure by Season

Spring included March, April, and May; summer, June, July, and August; autumn: September, October, and November; and winter: December, January, and February. The dotted lines indicate the lower and upper number of all treatment failure events in all groups across the 4 seasons (range, 3-7); the dashed line indicates the middle value of 5 treatment failure events (actual mean of the 10 within-range observations: 5.6). The physician assessment–based adjustment (PABA) group showed a significantly higher number of treatment failure events during autumn vs either the symptom-based adjustment (SBA) group or the biomarker-based adjustment (BBA) group.

[a] *P*=.02 for PABA vs BBA and SBA in autumn). We infer from these data that the expected number of treatment failure events for all 3 treatment modalities is typically 5 per 100 persons or about 5%, doubling to 10% to 11% in the autumn and winter within the PABA group.

Table 1

Demographics of Participants

	No. (%) by Adjustment Strategy			*P* Value
	Physician (n = 114)	Biomarker (n = 115)	Symptom (n = 113)	
Male sex	42 (36.8)	33 (28.7)	30 (26.5)	.21[a]
Race/ethnicity				
American Indian/Alaska Native	0	0	1 (0.9)	.03[a]
Asian/Pacific Islander	1 (0.9)	2 (1.7)	10 (8.8)	
Black	24 (21.1)	28 (24.3)	17 (15.0)	
White	76 (66.7)	71 (61.7)	69 (61.1)	
Hispanic	11 (9.6)	13 (11.3)	14 (12.4)	
Other[b]	2 (1.8)	1 (0.9)	2 (1.8)	
Skin test atopic status[c]	97 (85.1)	99 (86.1)	93 (82.3)	.70[a]
	Mean (SD)			
Age at visit 1, y	34.2 (11.9)	34.8 (11.3)	36.0 (12.2)	.52[d]
Duration of asthma (since first diagnosed), y	20.4 (10.4)	18.8 (10.3)	21.3 (12.1)	.21[d]
Height at visit 1, cm	168.7 (8.8)	168.4 (9.1)	168.1 (9.1)	.89[d]
Weight at visit 1, kg	80.2 (22.8)	82.7 (22.7)	77.1 (20.4)	.17[d]
Body mass index at visit 1[e]	28.2 (7.9)	29.0 (7.3)	27.1 (6.2)	.14[d]
Prebronchodilator FEV_1 At visit 4, L	3.03 (0.72)	2.94 (0.74)	2.90 (0.69)	.34[d]
% Predicted at visit 4	87.7 (12.1)	86.3 (10.4)	85.6 (11.0)	.37[d]
FEV_1 at visit 3 Albuterol (4 puffs) reversal, %	9.6 (6.5)	9.6 (5.5)	9.2 (5.8)	.81[d]
Postalbuterol (4 puffs), L	3.32 (0.75)	3.21 (0.81)	3.16 (0.71)	.31[d]
AM Peak flow 2-week average prior to visit 4, L/min	460.1 (111.3)	(n = 114) 442.8 (117.5)	436.9 (104.5)	.26[d]
PM Peak flow 2-week average prior to visit 4, L/min	466.5 (112.7)	(n = 114) 445.3 (118.2)	441.3 (104.0)	.19[d]
ACQ average score at visit 4[f]	0.72 (0.50)	0.79 (0.54)	0.73 (0.49)	.57[d]

	No. (%) by Adjustment Strategy			*P* Value
	Physician (n = 114)	Biomarker (n = 115)	Symptom (n = 113)	
AQLQ average score at visit 3[g]	(n = 112) 6.27 (0.76)	6.16 (0.77)	6.25 (0.72)	.48[d]
ASUI average score at visit 4[h]	0.90 (0.10)	0.88 (0.12)	0.90 (0.10)	.39[d]
Exhaled nitric oxide at visit 4, ppb[i]	(n = 108) 21.38 (0.62)	(n = 114) 18.88 (0.66)	(n = 110) 20.78 (0.54)	.28[j]
Imputed PC_{20} at visit 4, mg/mL[i]	(n = 99) 3.50 (1.43)	(n = 100) 2.37 (1.54)	(n = 98) 2.64 (1.27)	.14[j]
IgE at visit 2, IU/mL[i]	(n = 107) 130.0 (1.5)	(n = 105) 118.9 (1.4)	(n = 101) 133.8 (1.4)	.83[i]
	Median (IQR)			
Two-week average prior to visit 4 Daily symptoms[k]	0.05 (0-0.14)	(n = 114) 0.06 (0.01-0.21)	0.05 (0-0.20)	.26[l]
Albuterol rescue use (puffs)	0.04 (0-0.29)	(n = 114) 0.07 (0-0.43)	(n = 112) 0 (0-0.31)	.42[l]
Exhaled breath condensate pH at visit 4	8.52 (8.25-8.64)	(n = 110) 8.48 (8.29-8.60)	(n = 107) 8.47 (8.21-8.61)	.83[l]
Sputum eosinophils at visit 3	(n = 79) 0.40 (0-1.20)	(n = 67) 0.20 (0-0.80)	(n = 76) 0.40 (0-1.40)	.09[l]
Blood eosinophils at visit 2, /mm^3	(n = 111) 132.0 (100.0-222.0)	(n = 108) 178.5 (100.0-300.0)	(n = 108) 169.0 (100.0-224.0)	.17[l]

Abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality-of-Life Questionnaire; ASUI, Asthma Symptom Utility Index; FEV_1, forced expiratory volume in the first second of expiration; IgE, immunoglobulin E; MID, minimal clinically important difference; PC_{20}, provocative concentration of methacholine (<8 mg/mL) causing a 20% drop in FEV_1.

[a] Calculated using the Chisq test for differences in proportions among the 3 treatment groups.

[b] The National Institutes of Health did not require additional specification of other so this information was not collected.

[c] At least 1 positive skin test, using the prick-puncture method, and a panel of common aeroallergens.

[d] Calculated using the analysis of variance *F* test for differences among the 3 treatment groups.

[e] Calculated as weight in kilograms divided by height in meters squared.

[f] A higher score indicates worse asthma control (score range: 0-6; MID: 0.5).[15]

[g] A higher score indicates a better quality of life (score range: 1-7; MID: 0.5).[16]

[h] A higher score indicates better asthma control (score range: 0-1; MID: unknown, but a difference of 0.3 is suggested to distinguish between mild to moderate and moderate to severe asthma).

[i] Geometric mean coefficient of variation reported.

[j] Calculated using the analysis of variance *F* test for differences among the 3 treatment groups on a log scale.

[k] A higher score indicates a greater severity of symptoms (score range: 0-3).

[1] Calculated using the Kruskal-Wallis test for differences among the 3 treatment groups.

Table 2

Inhaled Steroid Dosing Adjustment

	Control Status	Inhaler Dose Change
Physician assessment-based adjustment (inhaler A)[a]		
FEV_1 ≥85% at baseline		
Plus symptoms in past 2 wk ≤2 d/wk (all AEQ scores of 0)	Well controlled	Down 1 level
Plus symptoms no worse than mild (AEQ scores of 0 or 1 on each question)	Controlled	Maintain current level
FEV_1 <85% at baseline, moderate symptoms (any AEQ score of 2 or 3), or meets criteria for treatment failure	Undercontrolled	Up 1 level
Biomarker-based adjustment (inhaler B)		
Fraction of exhaled nitric oxide, ppb		
<22	Well controlled	Down 1 level
22-35	Controlled	Maintain current level
>35	Undercontrolled	Up 1 level
Inhaled corticosteroids dose level[b]	**Dose, μg/d**	**Frequency**
1	None	
2	80 (2 puffs)	Once daily (am)
3	160 (2 puffs)	Twice daily
4	320 (4 puffs)	Twice daily
5	640 (8; 4 puffs at double strength)	Twice daily

Abbreviations: AEQ, Asthma Evaluation Questionnaire; FEV_1, forced expiratory volume in the first second of expiration.

[a]Physician was defined as the principal investigator or his/her physician designee, who used a clinical assessment tool similar to the US National Heart, Lung, and Blood Institute guidelines.

[b]All participants began the trial at level 3, from which therapy could be intensified or deintensified. The dose level was the prescribed therapy intensity.