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Daily versus As-Needed Corticosteroids for Mild Persistent Asthma

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ABSTRACT

BACKGROUND

Although guidelines recommend daily therapy for patients with mild persistent asthma, prescription patterns suggest that most such patients use these so-called controller therapies intermittently. In patients with mild persistent asthma, we evaluated the efficacy of intermittent short-course corticosteroid treatment guided by a symptom-based action plan alone or in addition to daily treatment with either inhaled budesonide or oral zafirlukast over a one-year period.

METHODS

In a double-blind trial, 225 adults underwent randomization. The primary outcome was morning peak expiratory flow (PEF). Other outcomes included the forced expiratory volume in one second (FEV_1) before and after bronchodilator treatment, the frequency of exacerbations, the degree of asthma control, the number of symptom-free days, and the quality of life.

RESULTS

The three treatments produced similar increases in morning PEF (7.1 to 8.3 percent; approximately 32 liters per minute; P=0.90) and similar rates of asthma exacerbations (P=0.24), even though the intermittent-treatment group took budesonide, on average, for only 0.5 week of the year. As compared with intermittent therapy or daily zafirlukast therapy, daily budesonide therapy produced greater improvements in pre-bronchodilator FEV_1 (P=0.005), bronchial reactivity (P<0.001), the percentage of eosinophils in sputum (P=0.007), exhaled nitric oxide levels (P=0.006), scores for asthma control (P<0.001), and the number of symptom-free days (P=0.03), but not in post-bronchodilator FEV_1 (P=0.29) or in the quality of life (P=0.18). Daily zafirlukast therapy did not differ significantly from intermittent treatment in any outcome measured.

CONCLUSIONS

It may be possible to treat mild persistent asthma with short, intermittent courses of inhaled or oral corticosteroids taken when symptoms worsen. Further studies are required to determine whether this novel approach to treatment should be recommended.

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Treatment guidelines recommend daily antiinflammatory therapy to control mild persistent asthma.[1,2] This recommendation for so-called controller therapy was prompted by studies reporting that such treatment improves physiological measures of airway obstruction (peak expiratory flow [PEF] and forced expiratory volume in one second [FEV_1]), the severity of symptoms, the frequency of exacerbations, and the quality of life[3-5] and was reinforced by reports that inhaled corticosteroid treatment may prevent progressive loss of pulmonary function.[6-8] However, analysis of pharmacy records suggests that most patients infrequently renew their prescriptions for controller medications (inhaled corticosteroids and leukotriene-receptor antagonists).[9]

We reasoned that patients with mild asthma may be using their treatment intermittently because they do not perceive the need for daily therapy. To analyze whether this strategy could be an acceptable approach to treatment in patients with mild persistent asthma, we modified a symptom-based action plan to guide the use of inhaled or oral corticosteroids when signs or symptoms of asthma worsened.[10] In a three-way study — the Improving Asthma Control (IMPACT) Trial — we compared the level of asthma control obtained with the use of this intermittent-treatment approach with that obtained with use of the intermittent-treatment plan plus daily treatment with a controller medication, either an inhaled corticosteroid (budesonide) or a leukotriene-receptor antagonist (zafirlukast). Morning PEF, a widely used and robust indicator of airflow obstruction, was the primary outcome indicator. Secondary outcomes included the frequency of asthma exacerbations, the number of days lost from work or school, the number of symptom-free days, asthma-related quality of life, and a panel of physiological and biologic measures of asthma activity.

METHODS

PATIENTS

Patients were recruited between February 2000 and May 2002 at six centers with the use of methods and equipment described previously.[11,12] The protocol was approved by the institutional review board of each center, and written informed consent was obtained from each participant. Inclusion criteria were physician-diagnosed asthma, an age of 18 to 65 years, and an FEV_1, measured more than four hours after the most recent use of a bronchodilator, that was at least 70 percent of the predicted value. All patients had an increase in the FEV_1 of at least 12 percent and at least 200 ml after the inhalation of albuterol or a fall in FEV_1 of at least 20 percent after inhaling a concentration of methacholine of less than 16 mg per milliliter (PC_{20}; lower concentrations indicate greater reactivity).

Exclusion criteria included cigarette smoking, respiratory tract infection or corticosteroid use in the previous six weeks, and hospitalization or two or more visits to the emergency department for asthma in the previous year. Patients qualifying at a screening visit were instructed in the use of an electronic peak flowmeter (AirWatch, ENACT Health Management Systems) and were given a diary to record morning and evening PEF, asthma symptoms, nocturnal awakenings related to asthma, and as-needed albuterol use. They were instructed to take one puff from a placebo-dispensing dry-powder inhaler (Turbuhaler, AstraZeneca), which was identical in appearance to the device used to dispense inhaled budesonide, and one placebo tablet (identical in appearance to zafirlukast) twice a day.

We enrolled patients only if their diary records and findings during visits in the next four weeks met the criteria for mild persistent asthma (self-treatment with a beta-agonist more than two days per week, nighttime awakenings related to asthma more than two days per month, or variability in the PEF of 20 to 30 percent). Apart from accepting a baseline FEV_1 as low as 70 percent of the predicted value, we excluded patients if they met any criteria for persistent moderate asthma (i.e., daily self-treatment with a beta-agonist, nighttime awakenings once a week, or more than 30 percent variability in PEF).[1] Enrollment also required at least 70 percent adherence to diary keeping, Turbuhaler use (by counting the number of doses remaining in the inhaler), and tablet use (established by pill counts and by electronic drug-exposure monitoring [eDEM, Aardex] of the time and date of each opening of the pill bottle).[13] PEF measurements were made and diaries were kept for four weeks during the run-in period, at the midpoint of the study, and at the end of the study.

PROTOCOL

On entry, all patients received 10 minutes of instruction in a symptom-based asthma treatment

plan (details of the plan are provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org). The plan called for patients to take open-label budesonide (800 μg twice daily) for 10 days or prednisone (0.5 mg per kilogram of body weight per day) for 5 days if their asthma symptoms worsened.[10] The patients' understanding of this plan was not formally evaluated, but they did receive a written summary of the plan, and the plan was reviewed briefly at each study visit.

After completing the run-in period, the patients were assigned to one of three parallel treatment groups: twice-daily oral placebo and inhalation of 200 μg of budesonide, twice-daily oral zafirlukast (20 mg) and inhalation of placebo, or twice-daily oral and inhaled placebo (intermittent treatment) (Fig. 1) (see the Supplementary Appendix for details of the procedures at visits). Treatment assignment was stratified according to center, and the use of an adaptive randomization scheme ensured balance with respect to PC_{20}, age, and racial or ethnic group.

Budesonide, zafirlukast, and matched placebos in identical delivery systems (pills or Turbuhaler) were donated by AstraZeneca. Representatives of the company reviewed and commented on the protocol but made no other contribution to its design, conduct, interpretation, or presentation.

The run-in and treatment phases both ended with a 10-to-14-day period of intense combined therapy, consisting of 0.5 mg of prednisone per kilogram per day, 800 μg of budesonide twice daily, and 20 mg of zafirlukast twice daily, plus treatment as needed with albuterol (540 to 720 μg), to eliminate any easily reversed causes of airflow obstruction affecting PEF or FEV_1.

At study visits, FEV_1 was measured, adherence to treatment was assessed, the degree of asthma control was assessed by means of a seven-item questionnaire (in which a score of 0 indicated no symptoms and a score of 6 severe symptoms),[14] medication-related side effects were assessed, and symptom-related impairment or discomfort was evaluated by means of the Asthma Symptom Utility

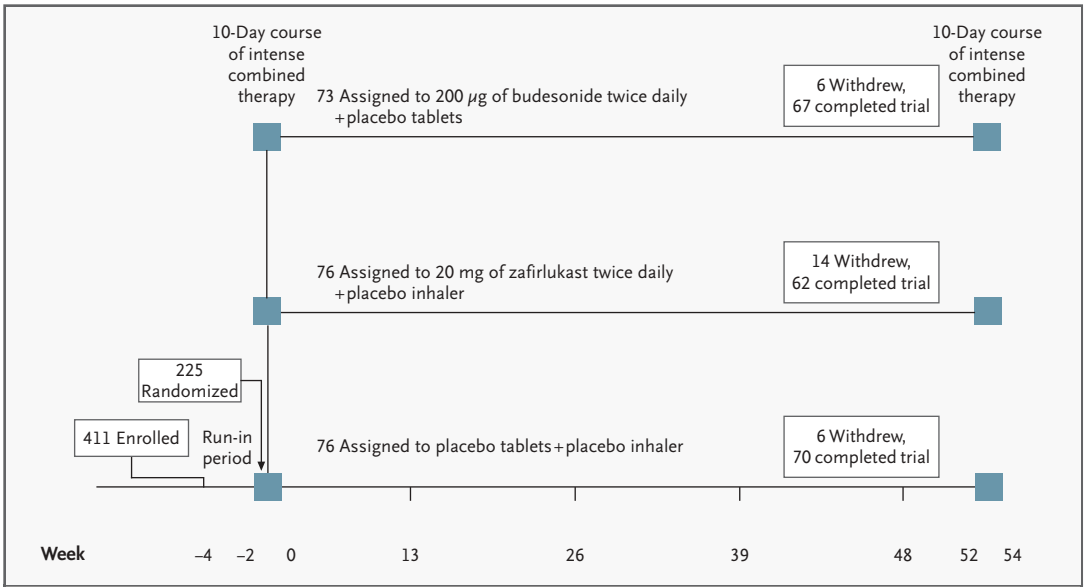

Figure 1. Enrollment and Outcome.

Reasons for exclusion during the run-in period were the need for inhaled budesonide therapy in 34 patients, excessive symptoms in 30, too few symptoms in 30, withdrawal of consent by 31, loss to follow-up of 19, failure to meet adherence criteria in 17, use of excluded medications by 6, presence of an excluded medical condition in 6, and other causes in 3. The run-in and treatment phases both ended with a 10-to-14-day period of intense combined therapy, consisting of 0.5 mg of prednisone per kilogram per day, 800 μg of budesonide twice daily, and 20 mg of zafirlukast twice daily, plus treatment with albuterol (540 to 720 μg), to eliminate any easily reversed causes of airflow obstruction affecting PEF or FEV_1.

Index.[15] The Asthma Symptom Utility Index is derived from a 10-item questionnaire completed by the patient. Scores range from 0 to 1, with higher scores indicating fewer symptoms. At visits during the periods in which diaries were maintained (four weeks during the run-in period and at the midpoint and end of the treatment periods, and during the two weeks of the two periods of intense combined treatment), peak flow was obtained from the diary records. Questionnaires about the number of symptom-free days, adverse events, and health care use were administered at all study visits and by means of telephone calls between visits. When these questionnaires identified patients who had had worsening of asthma symptoms, they were asked whether they had used the symptom-based action plan and this information was recorded.

The asthma-related quality of life was assessed by means of a questionnaire at enrollment and at the end of treatment[16]; patients rate the degree of impairment caused by asthma during the preceding 14 days and respond to each of the 32 items using a 7-point scale on which a score of 1 indicates maximal impairment and a score of 7 no impairment. Changes in the score of 0.5, 1.0, and 1.5 correspond to small, moderate, and large differences, respectively. The questionnaire can be used to provide an overall score and scores in four areas: limitation of activities, asthma symptoms, emotional functioning, and symptoms arising from environmental exposures. Exhaled nitric oxide, the PC_{20}, and the percentage of eosinophils in sputum were measured at enrollment and at the end of treatment (Fig. 1).

OUTCOME VARIABLES

The primary outcome variable was the change from baseline in two-week average morning PEF. Other objective outcome variables were the changes from baseline in the FEV_1 before bronchodilator use, the FEV_1 after treatment with 540 to 720 μg of albuterol, and the morning PEF during the period of intense combined therapy and FEV_1 after the period of intense combined therapy. We also measured the frequency of asthma exacerbations warranting the initiation of prednisone therapy according to the symptom-based action plan (whether initiated or not). Patients were instructed to notify their study center about these events, but we also identified such events by asking specific questions at study visits and during telephone contacts. Other patient-reported outcomes were responses to standard questionnaires on asthma control, asthma-related quality of life, symptom-free days, symptom-related impairment or discomfort, days missed from work or school, and adverse events (see above).

STATISTICAL ANALYSIS

The trial was designed to show the superiority of any one treatment over either of the other two. The primary outcomes were evaluated as the average percent change from the end of the run-in period to the end of treatment and were initially compared by means of analysis of variance. Pairwise comparisons between groups were evaluated if the P value for the overall test was less than 0.048 (by a two-sided test, adjusted for an interim analysis at the 0.005 level). These comparisons were then adjusted for baseline characteristics by including in an analysis-of-covariance model effects such as center, interaction between center and treatment, age, baseline PC_{20}, baseline FEV_1, duration of asthma, and other important baseline covariates listed in Table 1 (the list of covariates analyzed for each outcome is provided in the Supplementary Appendix). Repeated-measures analysis of covariance was also used on outcomes measured repeatedly throughout the study to evaluate correlated data.

The times to the first exacerbation of asthma were compared by means of Kaplan–Meier curves and the log-rank test. A repeated-measures proportional-hazards approach was used to compare groups, allowing for multiple exacerbations per patient.[17,18] The patient-reported outcomes regarding asthma control and symptoms throughout the trial were evaluated with repeated-measures analysis of covariance.

The primary end point compared among the groups was the change in morning PEF from randomization to the end of the trial. Using the standard deviation for morning PEF of 36.6 liters per minute noted in a previous study,[11] we calculated that a sample of 216 patients would provide a statistical power of 90 percent to detect the difference widely considered to be of clinical significance, 25 liters per minute, at a significance level of 4.8 percent, allowing a dropout rate of 15 percent. For the secondary end point — change in morning PEF from the first to the second period of intense combined therapy — we used the variability observed in the corticosteroid run-in period of a previous trial.[12] We calculated that if 199 patients completed the study, the study would have a statistical power of 80 percent to detect a difference of 21 liters

per minute in this morning PEF during the period of intense combined therapy between any two treatment groups. We further calculated that this sample would provide 80 percent power to detect a change of 13 liters per minute in morning PEF within groups.

RESULTS

Of 411 patients who were enrolled after screening, 225 underwent randomization and 199 completed the study (Fig. 1). The treatment groups were well matched (Table 1). Twenty-six patients withdrew after randomization, 6 each from the budesonide and intermittent-treatment groups and 14 from the zafirlukast group (P=0.10). Reasons for withdrawal included loss to follow-up (in six patients), pregnancy (four patients), personal constraints (four patients), side effects possibly related to study medications (two patients), dissatisfaction with asthma control (one patient), and miscellaneous reasons (nine patients).

Adherence to study medication regimens, estimated from counting unused doses in the Turbuhaler and from pill counts and eDEM records, exceeded 90 percent and was similar among the groups. The use of open-label budesonide was no greater in the intermittent-treatment group than in the groups taking daily budesonide or zafirlukast (Fig. 2). Inhaled budesonide was taken for only 55 percent of the episodes of mild-to-moderate worsening of symptoms as defined by the asthma action plan (Supplementary Appendix). The average per-patient use of a daily controller medication over the year of the study was 47.8 weeks for the budesonide and zafirlukast groups (92 percent adherence × 52 weeks) and 0.48 week for the intermittent-treatment group.

The primary outcome, the change in morning PEF from the final two weeks of the run-in period to the final two weeks of the year of treatment, did not differ significantly among the groups, increasing about 7.8 percent (32 liters per minute) in all groups (P=0.90) (Table 2). The increases in average morning PEF from the first to the second period of intense combined therapy were also similar among the groups (3.5 to 5.7 percent, P=0.61) (Table 2), even after adjustment for center, age, minority status, and PC_{20}.

The pre-bronchodilator FEV_1 increased more in the budesonide group than in the other two groups (P=0.005) (Table 2), but the changes in

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Daily Budesonide (N=73)	Daily Zafirlukast (N=76)	Intermittent Therapy (N=76)
Male sex — no. (%)	25 (34)	29 (38)	33 (43)
Minority — no. (%)†‡	13 (18)	26 (34)	22 (29)
Black race — no. (%)†	9 (12)	11 (14)	13 (17)
Age — yr	33.2±9.5	33.6±11.1	32.0±10.5
Duration of asthma — yr	17.1±11.0	20.9±13.1	19.5±11.8
Data missing — no. of patients	2	2	5
Height — cm	170.0±10.4	170.3±8.9	170.2±9.6
Weight — kg	74.3±15.3	77.1±16.6	74.6±15.4
Body-mass index	25.7±4.4	26.5±5.0	25.7±4.6
Pre-bronchodilator FEV_1			
Liters	3.2±0.8	3.2±0.8	3.2±0.7
% Predicted	90.5±12.6	88.2±14.4	87.8±12.7
Morning PEF, 2-wk average — liters/min	467±117	468±111	462±106
PC_{20} — mg/ml§	1.08±1.25	1.33±1.43	1.17±1.22
Data missing — no. of patients	2	3	1
Exhaled nitric oxide — parts per billion			
Median	16.8	16.8	16.4
Interquartile range	11.7–25.1	10.5–24.9	10.3–23.5
Data missing — no. of patients	4	3	3
Sputum eosinophils — %			
Median	0.6	0.5	0.4
Interquartile range	0.2–2.0	0.0–1.3	0.0–1.3
Data missing — no. of patients	32	35	35
Asthma Quality of Life score¶	5.8±0.7	5.8±0.6	5.9±0.6
Asthma-control score‖	1.1±0.6	1.1±0.5	1.1±0.5
No. of symptom-free days in past 14 days	5.9±4.4	5.5±4.2	6.1±4.3
Asthma Symptom Utility Index score**	0.8±0.1	0.8±0.1	0.8±0.1

* Plus–minus values are means ±SD. To convert values for weight to pounds, multiply by 2.2. Body-mass index is the weight in kilograms divided by the square of the height in meters.
† Minority status and black race were self-reported.
‡ P=0.07 by the chi-square test.
§ Geometric means and coefficients of variation are given.
¶ Scores can range from 1 (totally limited) to 7 (not at all limited).
‖ Scores can range from 0 (no symptoms) to 6 (severe symptoms).
** Scores can range from 0 to 1, with higher scores indicating fewer symptoms.

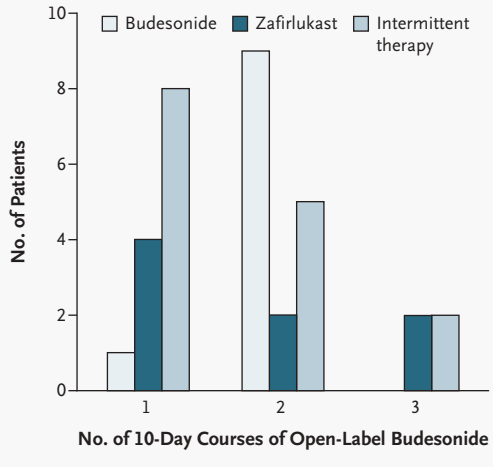

Figure 2. Number of 10-Day Courses of Open-Label Budesonide Initiated by Patients in Each Group, as Guided by the Symptom-Based Action Plan.

post-bronchodilator FEV_1 did not differ significantly among the groups (P=0.29) (Table 2). The average changes in post-bronchodilator FEV_1 in the budesonide and intermittent-treatment groups were −1.7 percent and −1.0 percent, respectively, resulting in an average difference between groups of −0.7 percentage point. The 95 percent confidence interval for this difference was −2.1 percent (i.e., greater decrease in the budesonide group) to 0.7 percent (greater decrease in the intermittent-treatment group).

The change in post-bronchodilator FEV_1 in the 46 patients with an FEV_1 at entry that was 70 to 79 percent of the predicted value was not significantly different from that in the 144 patients with an FEV_1 at entry that was at least 80 percent of the predicted value (P=0.59) (data not shown). The FEV_1 measured after the period of intense combined therapy declined similarly in all groups. Patients treated with budesonide had greater improvements in the percentage of eosinophils in sputum, exhaled nitric oxide values, and PC_{20} values than did the patients in either of the other two groups (Table 2). As compared with intermittent treatment, treatment with zafirlukast produced no significantly greater improvement in any outcome.

Thirty exacerbations of symptoms warranting treatment with prednisone occurred in 25 (11.1 percent) patients, an overall rate of 0.13 per patient-year. The proportion of patients who had one or more exacerbations did not differ significantly among the groups (one exacerbation in eight patients in the budesonide group and three in two patients in this group; one exacerbation in six patients in the zafirlukast group; and one exacerbation in seven patients in the intermittent-treatment group and three in one patient in this group).

Kaplan–Meier curves showed no significant differences among the groups, whether they were plotted as the time to a first event (P=0.39 by the log-rank test) (Fig. 3) or allowed multiple events per patient (P=0.24). The 12-month Kaplan–Meier exacerbation rates for the budesonide and intermittent-treatment groups were 16.1 percent and 11.3 percent, respectively, resulting in an average difference (i.e., positive sign indicates more exacerbations in the budesonide group) of +4.8 percentage points. The 95 percent confidence interval for this difference was −7 percent (lower in the budesonide group) to 16 percent (higher in the budesonide group). Patients initiated prednisone treatment for only 36.7 percent of the episodes (5 of 14 episodes in the budesonide group, 2 of 6 in the zafirlukast group, and 4 of 10 in the intermittent-treatment group). Five exacerbations required a visit to the emergency department (three in the budesonide group and one each in the other two groups). None warranted hospitalization. Altogether, patients missed 13 days from work or school because of asthma (7 days in the budesonide group, 2 days in the zafirlukast group, and 4 days in the intermittent-treatment group; P=0.18).

Of the patient-reported outcomes, the improvements in the asthma control score and in the number of symptom-free days were significantly greater with budesonide treatment than with either zafirlukast or intermittent treatment, which did not differ significantly from each other (Table 2). The greater number of symptom-free days over a 2-week period with budesonide (9.9 days) than with zafirlukast (8.7 days) or intermittent treatment (8.8 days) translates to 26 additional symptom-free days per year (95 percent confidence interval, 1.8 to 48.5). This was not associated, however, with any difference in the changes in the scores for the asthma-related quality of life, which improved in all groups (Table 2).

Neither the overall frequency of adverse events nor the frequency of severe events (36 or 37 in each group) differed significantly among the groups; seven of the patients with severe events required hospitalization. In this blinded study, no hospital-

Table 2. Average Changes in Primary and Secondary Outcome Measures over a One-Year Period.*

Outcome	Daily Budesonide			Daily Zafirlukast			Intermittent Treatment			Overall P Value†
	No. of Patients	Value	Within-Group P Value	No. of Patients	Value	Within-Group P Value	No. of Patients	Value	Within-Group P Value	
Morning PEF (%)	66	8.3±1.9	<0.001	62	7.9±2.1	<0.001	70	7.1±2.0	<0.001	0.90
Morning PEF post-PICT (%)	66	5.7±1.7	0.002	62	5.6±1.8	0.002	69	3.5±1.7	0.05	0.61
FEV_1 (%)										
Pre-bronchodilator	67	4.0±1.2	0.001	62	−1.1±1.0	0.30	70	0.7±1.1	0.55	0.005
Post-bronchodilator	67	−1.7±0.5	0.002	61	−0.5±0.7	0.45	69	−1.0±0.5	0.04	0.29
Post-PICT	67	−1.5±0.7	0.03	62	−2.1±0.7	0.003	68	−0.6±0.6	0.34	0.27
Exhaled nitric oxide (%)	63		0.75	60		0.02	66		<0.001	0.006
Median		−14.4			12.4			26.6		
Interquartile range		−44.4 to 46.8		62	−24.6 to 82.8			−9.6 to 99.3	<0.001	
Sputum eosinophils (%)	34		0.03	26		0.71	35		0.03	0.007
Median		−0.3			0.0			0.2		
Interquartile range		−1.6 to 0.2			−0.9 to 0.3			−0.1 to 1.5		
PC_{20} (log_2)	63	1.8±0.2	<0.001	58	0.3±0.2	0.11	67	0.1±0.2	0.48	<0.001
Asthma Quality of Life score‡§	67	0.5±0.1	<0.001	64	0.3±0.1	<0.001	70	0.3±0.1	<0.001	0.18
Asthma control score‡¶	70	−0.4±0.1	<0.001	70	−0.2±0.04	<0.001	73	−0.3±0.05	<0.001	<0.001
No. of symptom-free days‡	70	4.0±0.4	<0.001	70	3.1±0.4	0.001	73	2.9±0.4	<0.001	0.03
Asthma Symptom Utility Index‡‖	70	0.06±0.01	<0.001	70	0.04±0.01	0.002	73	0.04±0.01	<0.001	0.06

* Unless otherwise stated, values reflect mean (±SE) changes from baseline to the end of the treatment period (before the period of intense combined therapy [PICT]) (see Fig. 1). In each analysis of covariance model evaluated to confirm the unadjusted results above, the covariates used in the stratified randomization scheme of the study were included (center, age, minority status, and PC_{20} value). All other baseline covariates listed in Table 1 were then considered to see whether they added any significant explanatory power to the model. In the resulting main-effects models, the interaction between center and treatment and all pairwise interaction terms of the predictors in each model were also considered. The results based on the inclusion of these factors in each model did not differ significantly from the conclusions of the unadjusted results reported above.

† P values refer to differences among the groups with the use of analysis of variance or repeated-measures analysis of covariance.

‡ Results are mean changes from baseline averaged over all visits; P values are from longitudinal analysis (repeated-measures analysis of covariance).

§ Scores can range from 1 (totally limited) to 7 (not at all limited).

¶ Scores can range from 0 (no symptoms) to 6 (severe symptoms).

‖ Scores can range from 0 to 1, with higher scores indicating fewer symptoms.

ization was deemed by the investigators as being related to the study, study medication, or asthma.

DISCUSSION

Our study of 225 patients with mild persistent asthma showed no clinically significant difference among the three treatment groups with respect to morning PEF. Although other objective measures of lung function and airway biology were improved and patients reported 26 more days free from symptoms of asthma per year when treated with budesonide on a daily basis than with the other treatments, the frequency of asthma exacerbations did not dif-

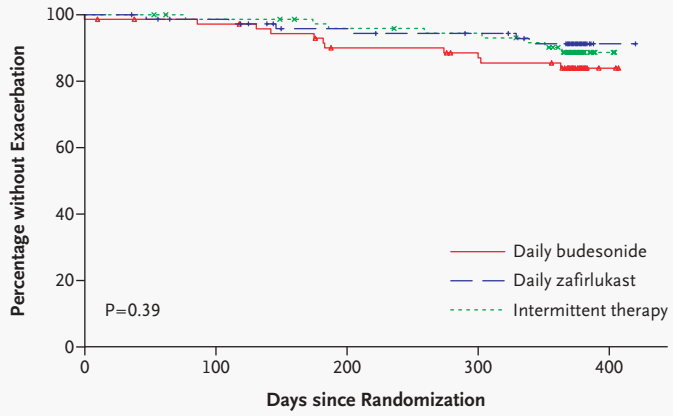

Figure 3. Kaplan–Meier Estimates of the Time to a First Exacerbation of Asthma.
There was no significant difference among the groups (P=0.39).

fer significantly among the groups. Although our study was not designed as a noninferiority trial and, thus, the findings must be considered preliminary, these data suggest that a novel approach to the treatment of persistent asthma — symptom-driven intermittent treatment with inhaled or oral corticosteroids — may be possible. Since the intermittent use of inhaled corticosteroids could decrease the adverse effects of these agents,[19] our data provide the impetus for a large-scale trial to test this novel approach to asthma treatment.

Epidemiologic studies have reported that the use of inhaled corticosteroids reduces asthma-related hospitalizations and deaths,[20,21] and some previous clinical studies of mild asthma have reported that inhaled corticosteroid therapy reduces the frequency of exacerbations and the rate of decline in the results of tests of airway caliber (PEF, FEV_1, or post-bronchodilator FEV_1),[3-5] so the suggestion that a large subgroup of patients with asthma may not require daily controller treatment will arouse concern.

However, the protective effect in the epidemiologic studies was most apparent by far in patients using frequent doses of an inhaled beta-agonist,[20] a pattern inconsistent with the criteria for mild persistent asthma. In our study of 411 patients who appeared on original screening to meet the criteria for mild persistent asthma, 64 were found to have asthma that was too severe and 30 asthma that was too mild to qualify. We believe that the lack of a difference among our treatment groups may reflect the low rate of exacerbations in patients who consistently meet the criteria for mild persistent asthma. This possibility is supported by our finding of a rate of exacerbations warranting prednisone treatment in our intermittent-treatment group (0.11 per patient-year) well below the rates reported in previous studies of mild asthma (0.21 to 0.77 per patient-year).[3-5]

This difference in asthma severity could also account for the difference from previous studies reporting that continuous corticosteroid therapy prevented a decline in airway function in patients with mild asthma.[3-5] We found no treatment-attributable difference in the change in post-bronchodilator FEV_1. Our study was shorter than the previous studies, but the preponderance of the differences between treatment groups in these studies occurred during the first year, and we noted no such effect. Our findings are consistent with those of the Childhood Asthma Management Program trial, a study of children with asthma, which showed no effect of five years of treatment with an inhaled corticosteroid on the change in post-bronchodilator FEV_1.[22] Furthermore, the robustness of our findings, as reflected by the confidence intervals for the differences in the decline in post-bronchodilator FEV_1 and in exacerbation rates, suggests that the treatment benefits that our study might have missed may be so small as not to justify the expense, potential adverse effects, and inconvenience of daily treatment with a controller therapy of all patients with mild persistent asthma.

We did find that budesonide (but not zafirlukast) improved markers of airway inflammation, such as bronchial reactivity, the percentage of eosinophils in sputum, and exhaled nitric oxide. It is noteworthy, however, that low-grade inflammation similar to that seen in our patients has been reported in patients with spontaneous, complete, sustained clinical remission of asthma,[23,24] who are not now considered candidates for daily controller treatment.

We found that daily treatment with budesonide (but not zafirlukast) was associated with a significant increase in the number of symptom-free days and a trend toward improvement in the scores for a weighted symptom utility index, but not in asthma-related quality of life. This lack of improvement in the quality of life may reflect the light burden of symptoms of mild asthma. In asthma of this severity, symptoms are occasional and are usually promptly relieved by treatment with an inhaled bronchodilator. Whether the increase in symptom-free days is worth the costs of treatment, both fiscal and

with respect to long-term side effects, may thus be an individual, subjective judgment best left to the patient and his or her health care provider.[19]

It is fair to ask whether the approach to treatment in our intermittent-treatment group could be practically applied outside of the artificial conditions of a clinical trial. We tried to mimic true clinical conditions by basing the action plan on symptoms, rather than on peak flow. All our patients were given an open-label budesonide inhaler, prednisone tablets, and 10 minutes of instruction in the symptom-based action plan. This instruction was reinforced by a written summary and by reminders of the plan at each visit and a telephone call (every six weeks). This attention to teaching an action plan might limit the generalizability of our findings. However, even under these conditions, patients took budesonide for only 55 percent of the episodes of mild-to-moderate worsening of symptoms and prednisone for only 37 percent of the episodes severe enough to warrant its use. We also found no significant difference in the rate of exacerbations warranting prednisone treatment in patients who should have but did not take budesonide (7 of 22) than in those who should have and did (15 of 21). Taken together, these observations suggest that close, formal adherence to the action plan may not have accounted for our findings.

In adults with long-standing, mild persistent asthma who were given medication and instructed to initiate corticosteroid therapy according to a symptom-based action plan, regularly scheduled controller treatment with either inhaled budesonide or oral zafirlukast had no significant effect on the rate of severe exacerbations, impairment in the quality of life, or the rate of loss of pulmonary function over a period of one year. These findings suggest that the novel approach of treating patients with mild persistent asthma with inhaled and oral corticosteroids as needed may be viable. Longer and larger studies will be needed before this approach to asthma treatment can be recommended.

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