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 (FEV₁) 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 FEV₁ (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 FEV₁ (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.
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 \([\text{FEV}}_1]\)), 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 \(\text{FEV}_1\), 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 \(\text{FEV}_1\) of at least 12 percent and at least 200 ml after the inhalation of albuterol or a fall in \(\text{FEV}_1\) 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 \(\text{FEV}_1\) 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. 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 PC20, 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 FEV1.

At study visits, FEV1 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), 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 FEV1.
FEV₁ baseline in the FEV₁ objective outcome variables were the changes from
The primary outcome variable was the change from
ment (Fig. 1).
mental exposures.
maximal impairment and a score of 7 no impair-
patients rate the degree of
Changes in the score of 0.5, 1.0, and 1.5 cor-
respond to small, moderate, and large differences, respectively. The questionnaire can be used to pro-
vide 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 PC₂₀,
and the percentage of eosinophils in sputum were measured at enrollment and at the end of treat-
ment (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 FEV₁ before bronchodilator use, the
FEV₁ after treatment with 540 to 720 μg of albuterol,
and the morning PEF during the period of intense
combined therapy and FEV₁ after the period of in-
tense combined therapy. We also measured the fre-
quency of asthma exacerbations warranting the ini-
tiation 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-relat-
ed 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 compar-
isons between groups were evaluated if the P value
for the overall test was less than 0.048 (by a two-sid-
etest, 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, inter-
action between center and treatment, age, baseline
PC₂₀, baseline FEV₁, duration of asthma, and other
important baseline covariates listed in Table 1 (the
list of covariates analyzed for each outcome is pro-
vided in the Supplementary Appendix). Repeat-
ed-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 pro-
portional-hazards approach was used to compare
groups, allowing for multiple exacerbations per pa-
tient. The patient-reported outcomes regarding
asthma control and symptoms throughout the
trial were evaluated with repeated-measures analy-
sis of covariance.

The primary end point compared among the
groups was the change in morning PEF from ran-
donization to the end of the trial. Using the stan-
dard deviation for morning PEF of 36.6 liters per
minute noted in a previous study, we calculated
that a sample of 216 patients would provide a sta-
tistical 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 com-
bined therapy — we used the variability observed
in the corticosteroid run-in period of a previous
trial. We calculated that if 199 patients complet-
ed the study, the study would have a statistical pow-
er of 80 percent to detect a difference of 21 liters
daily vs. as-needed therapy for mild persistent asthma

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\textsubscript{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.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Daily Budesonide (N=73)</th>
<th>Daily Zafirlukast (N=76)</th>
<th>Intermittent Therapy (N=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex — no. (%)</td>
<td>25 (34)</td>
<td>29 (38)</td>
<td>33 (43)</td>
</tr>
<tr>
<td>Minority — no. (%)</td>
<td>13 (18)</td>
<td>26 (34)</td>
<td>22 (29)</td>
</tr>
<tr>
<td>Black race — no. (%)</td>
<td>9 (12)</td>
<td>11 (14)</td>
<td>13 (17)</td>
</tr>
<tr>
<td>Age — yr</td>
<td>33.2±9.5</td>
<td>33.6±11.1</td>
<td>32.0±10.5</td>
</tr>
<tr>
<td>Duration of asthma — yr</td>
<td>17.1±11.0</td>
<td>20.9±13.1</td>
<td>19.5±11.8</td>
</tr>
<tr>
<td>Data missing — no. of patients</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Height — cm</td>
<td>170.0±10.4</td>
<td>170.3±8.9</td>
<td>170.2±9.6</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>74.3±15.3</td>
<td>77.1±16.6</td>
<td>74.6±15.4</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>25.7±4.4</td>
<td>26.5±5.0</td>
<td>25.7±4.6</td>
</tr>
<tr>
<td>Pre-bronchodilator FEV\textsubscript{1}</td>
<td>3.2±0.8</td>
<td>3.2±0.8</td>
<td>3.2±0.8</td>
</tr>
<tr>
<td>% Predicted</td>
<td>90.5±12.6</td>
<td>88.2±14.4</td>
<td>87.8±12.7</td>
</tr>
<tr>
<td>Morning PEF, 2-wk average — liters/min</td>
<td>467±117</td>
<td>468±111</td>
<td>462±106</td>
</tr>
<tr>
<td>Data missing — no. of patients</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Exhaled nitric oxide — parts per billion</td>
<td>1.08±0.15</td>
<td>1.33±0.43</td>
<td>1.17±1.22</td>
</tr>
<tr>
<td>Sputum eosinophils — %</td>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Asthma Quality of Life score</td>
<td>5.8±0.7</td>
<td>5.8±0.6</td>
<td>5.9±0.6</td>
</tr>
<tr>
<td>Asthma-control score</td>
<td>1.1±0.6</td>
<td>1.1±0.5</td>
<td>1.1±0.5</td>
</tr>
<tr>
<td>No. of symptom-free days in past 14 days</td>
<td>5.9±4.4</td>
<td>5.5±4.2</td>
<td>6.1±4.3</td>
</tr>
<tr>
<td>Asthma Symptom Utility Index score**</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
</tr>
</tbody>
</table>

* 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).
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The change in post-bronchodilator $\text{FEV}_1$ in the 46 patients with an $\text{FEV}_1$ at entry that was 70 to 79 percent of the predicted value was not significantly different from that in the 144 patients with an $\text{FEV}_1$ at entry that was at least 80 percent of the predicted value ($P=0.59$) (data not shown). The $\text{FEV}_1$ 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 $\text{PC}_{20}$ 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 $-3.7$ percent (lower in the budesonide group) to 16.1 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-
Daily vs. As-needed Therapy for Mild Persistent Asthma

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-

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Daily Budesonide</th>
<th>Daily Zafirlukast</th>
<th>Intermittent Treatment</th>
<th>Overall P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Value</td>
<td>Within-Group P Value</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Morning PEF (%)</td>
<td>66</td>
<td>8.3±1.9</td>
<td>&lt;0.001</td>
<td>62</td>
</tr>
<tr>
<td>Morning PEF post-PICT (%)</td>
<td>66</td>
<td>5.7±1.7</td>
<td>0.002</td>
<td>62</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-bronchodilator</td>
<td>67</td>
<td>4.0±1.2</td>
<td>0.001</td>
<td>62</td>
</tr>
<tr>
<td>Post-bronchodilator</td>
<td>67</td>
<td>−1.7±0.5</td>
<td>0.002</td>
<td>61</td>
</tr>
<tr>
<td>Post-PICT</td>
<td>67</td>
<td>−1.5±0.7</td>
<td>0.03</td>
<td>62</td>
</tr>
<tr>
<td>Exhaled nitric oxide (%)</td>
<td>63</td>
<td>0.75</td>
<td>0.02</td>
<td>60</td>
</tr>
<tr>
<td>Median</td>
<td>−14.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>−44.4 to 46.8</td>
<td>−24.6 to 82.8</td>
<td>−9.6 to 99.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sputum eosinophils (%)</td>
<td>34</td>
<td>0.03</td>
<td>0.71</td>
<td>26</td>
</tr>
<tr>
<td>Median</td>
<td>−0.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>−1.6 to 0.2</td>
<td>−0.9 to 0.3</td>
<td>−0.1 to 1.5</td>
<td></td>
</tr>
<tr>
<td>PC20 (log2)</td>
<td>63</td>
<td>1.8±0.2</td>
<td>&lt;0.001</td>
<td>58</td>
</tr>
<tr>
<td>Asthma Quality of Life score†‡</td>
<td>67</td>
<td>0.5±0.1</td>
<td>&lt;0.001</td>
<td>64</td>
</tr>
<tr>
<td>Asthma control score‡¶</td>
<td>70</td>
<td>−0.4±0.1</td>
<td>&lt;0.001</td>
<td>70</td>
</tr>
<tr>
<td>No. of symptom-free days‡</td>
<td>70</td>
<td>4.0±0.4</td>
<td>&lt;0.001</td>
<td>70</td>
</tr>
<tr>
<td>Asthma Symptom Utility Index‡¶</td>
<td>70</td>
<td>0.06±0.01</td>
<td>&lt;0.001</td>
<td>70</td>
</tr>
</tbody>
</table>

* 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 PC20 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.
There was no significant difference among the groups (P=0.39).

Figure 3. Kaplan–Meier Estimates of the Time to a First Exacerbation of Asthma. Percentage without Exacerbation 100 20 40 60 80 0

Days since Randomization

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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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