

Oral corticosteroids in poorly controlled asthma

To the Editor:

Clinicians expect that a short course of oral corticosteroids in patients with poorly controlled asthma should rapidly improve lung function, minimize symptoms, and reduce use of inhaled short-acting β -agonists.¹ However, data on the response to oral corticosteroids in poorly controlled asthma are generally lacking. During the clinical development of an inhaled corticosteroid, 2 separate, similarly designed clinical trials were performed for registration purposes, incorporating an initial oral corticosteroid treatment phase of patients with poorly controlled asthma.^{2,3} Pooling of the data from these 2 studies allowed a retrospective analysis of the morning peak expiratory flow (PEF) and symptom response to a short course of oral corticosteroids in a large group of patients with poorly controlled asthma.

Patients entered into the trials had a history of asthma, a morning PEF of 50% to 85% predicted and a $\geq 15\%$ increase in FEV₁ after use of an inhaled short-acting β -agonist. Patients with poorly controlled asthma (defined as either asthma-related nighttime sleep disturbances on at least 1 night, moderate daytime asthma symptoms on at least 3 days, or inhaled short-acting β -agonist use for symptom relief at least twice daily on all 5 days) identified during the last 5 days of the run-in period were treated with 30 mg of either oral prednisone (US) or prednisolone (United Kingdom) given once daily in the morning for 7 to 12 days.

Data from diary cards completed during the run-in and oral corticosteroid treatment periods for the 2 trials were pooled. The percent change in morning PEF with oral corticosteroids was calculated from the mean morning PEF over the period of the last 3 days of the oral corticosteroid treatment period and the mean morning PEF over the period of the last 5 days of run-in. Changes in wheeze score, nighttime asthma sleep disturbance score, and inhaled short-acting β -agonist use were calculated similarly and were compared between the patients with a $\geq 15\%$ improvement in morning PEF and those with a $<15\%$ improvement after oral corticosteroids by using the *t* test.

A total of 1293 patients were screened for entry into these 2 studies, and 784 patients were treated with oral corticosteroids. There was a mean increase of $17.6\% \pm 11.9\%$ SD in morning PEF after oral corticosteroids (Fig 1). There were 580 of 784 patients (74.0%) who had a $\geq 15\%$ improvement in morning PEF and 102 of 784 (13.0%) who had a $\geq 30\%$ improvement in morning PEF. The remaining 204 of 784 (26.0%) patients had a $<15\%$ improvement in morning PEF. The demographics, baseline characteristics, and use of inhaled corticosteroids at screen for the patients with a $\geq 15\%$ improvement in morning PEF and those with a $<15\%$ improvement were similar (Table I). Daytime asthma symptom scores and nighttime

Change from Run-in After Oral Corticosteroids

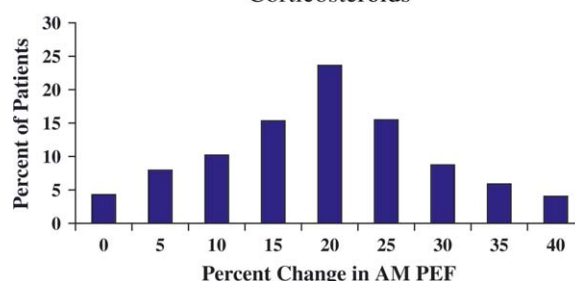


FIG 1. The 784 patients who received oral corticosteroid treatment are categorized by their percent change in morning (AM) PEF. Percent change in AM PEF was calculated from the mean AM PEF over the period of the last 3 days of the oral corticosteroid treatment period and the mean AM PEF over the period of the last 5 days of run-in.

asthma-related sleep disturbances improved and use of inhaled short-acting β -agonist decreased after oral corticosteroid treatment, but symptoms and β -agonist use changed significantly more in patients with a $\geq 15\%$ improvement in morning PEF. By multivariate analysis, patients with a history of allergy, an age <35 years, a higher screening morning PEF percent predicted, more frequent nighttime asthma-related sleep disturbances, and more frequent daily use of inhaled short-acting β -agonists for symptom relief were more likely to have a $\geq 15\%$ improvement in morning PEF.

In 468 patients, morning plasma cortisol levels were obtained before and after oral corticosteroid treatment. Median plasma cortisol levels fell significantly from 436.1 nmol/L (95% CI, 201.5-1078.0) at screen to 254.1 nmol/L (95% CI, 27.6-648.0) after oral corticosteroid treatment.

In this retrospective analysis, the morning PEF response to a course of oral corticosteroids in poorly controlled asthma followed a unimodal, normal distribution with a mean increase of $17.6\% (\pm 11.9\% \text{ SD})$. Basing a definition of corticosteroid resistance on a threshold increase in morning PEF of $<15\%$ would have resulted in 26% of the patients in this data set having been identified as corticosteroid-resistant. It was expected that this patient population would have responded to oral corticosteroids, because patients entered into the studies had both meaningful airflow obstruction and documented FEV₁ reversibility with use of an inhaled short-acting β -agonist. The factors associated with a reduced response to oral corticosteroids in poorly controlled asthma are not well understood. Unlike the findings in this analysis, previous work has shown that severe nocturnal symptoms, more frequent use of inhaled short-acting β -agonists, and gastroesophageal reflux have been associated with resistance to the effects of oral corticosteroids.⁴ Proportionally more patients with a screening morning PEF between 60% and 80% predicted and $>80\%$ predicted were responders than nonresponders. Whether this

TABLE I. Demographics, baseline characteristics and use of inhaled corticosteroids of patients who had a $\geq 15\%$ improvement and a $<15\%$ improvement in morning PEF after a short course of oral corticosteroids

	$\geq 15\%$ Improvement in morning PEF (n = 580)	$<15\%$ Improvement in morning PEF (n = 204)
Age (y)	36.5	39.5
Race (white/nonwhite)	543/37 (94%/6%)	195/9 (96%/4%)
Gender (male/female)	264/316 (46%/54%)	98/106 (48%/52%)
Screen morning PEF % predicted (mean)	67.2	70.9
Screen inhaled corticosteroid dose ¹		
None	218 (38%)	75 (37%)
Low	277 (48%)	96 (47%)
Medium	69 (12%)	26 (13%)
High	16 (3%)	7 (3%)

indicates a certain degree of fixed airway obstruction in the nonresponders, especially those with a morning PEF $<60\%$ predicted, is unclear. Information on other clinical characteristics previously associated with resistance to the effects of oral corticosteroids, such as exercise-induced bronchoconstriction, life-threatening exacerbations, sinusitis, and continued allergen exposure,⁴ was not available in this database. Chan et al⁵ have noted a higher rate of corticosteroid resistance in African Americans, but the percentage of nonwhites with a $<15\%$ improvement in morning PEF after oral corticosteroids was similar to the responders in this analysis.

Compliance with use of oral corticosteroids in these studies was high, as assessed by pill counts. Although pill counts may not be an accurate indicator of compliance, the significant fall in plasma cortisol levels supported good compliance with prednisone use. Of note, however, median plasma cortisol levels were within the lower end of the normal range for a morning value (≥ 200 nmol/L) after oral corticosteroids, indicating that a single morning plasma cortisol level is not an accurate reflection of adrenal suppression by exogenous corticosteroids. Changes in morning PEF were similar in patients with a normal and a suppressed plasma cortisol after a course of oral corticosteroids.

Strengths of this analysis were that patients with poorly controlled asthma were identified during a structured run-in period. Assessments of lung function were based on morning PEF averaged over several days, which possibly provided more reliable estimates of changes than a single measurement. Although there is no clear consensus on the dose and duration of treatment constituting an adequate short course of oral corticosteroids, a dose of 30 mg/day of prednisolone or prednisone for 7 to 12 days conforms to current asthma management guidelines.¹ The studies included a large number of patients seen in diverse clinical settings, both in academic and private practices in Europe and the United States. Use of inhaled long-acting β -agonists was not allowed during the oral corticosteroid treatment period, in accord with standard practice at the time. Patients were entered who had been on varying doses of inhaled corticosteroids. Previous use and dose of inhaled corticosteroids did not seem to influence the morning PEF response to oral corticosteroids.

In summary, this retrospective analysis revealed a wide range of morning PEF responses to a short course of oral corticosteroids in a large series of patients with poorly controlled asthma. Future studies are needed to define better the factors that affect the response to oral corticosteroids.

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