

Inhaled mometasone furoate reduces oral prednisone requirements while improving respiratory function and health-related quality of life in patients with severe persistent asthma

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Background: Inhaled corticosteroid therapy in severe persistent asthma has been shown to reduce or eliminate oral corticosteroid (OCS) use while retaining effective asthma control.

Objective: We sought to evaluate the ability of mometasone furoate (MF) delivered by means of dry powder inhaler to reduce daily oral prednisone requirements in OCS-dependent patients with severe persistent asthma.

Methods: We performed a 12-week, double-blind, placebo-controlled trial (21 centers, 132 patients) comparing 2 doses of

MF (400 and 800 µg administered twice daily) with placebo, followed by a 9-month open-label phase in which 128 patients received treatment with MF.

Results: At the endpoint of the double-blind trial, MF 400 and 800 mg twice daily reduced daily OCS requirements by 46.0% and 23.9%, respectively, whereas placebo increased OCS requirements by 164.4% ($P < .01$). Oral steroids were eliminated in 40%, 37%, and 0% of patients in the MF 400 and 800 mg twice daily and placebo groups, respectively. Pulmonary function and quality of life significantly increased for MF-treated patients. Further reductions in OCS requirements were achieved with long-term MF treatment in the open-label phase.

Conclusion: MF inhaled orally as a dry powder is an effective alternative to systemic corticosteroids in patients with severe persistent asthma. (*J Allergy Clin Immunol* 2000;106:852-60.)

Key words: Mometasone furoate, severe persistent asthma, oral corticosteroid-dependent asthma, prednisone, glucocorticoid, health-related quality of life, steroid sparing

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Although topical inhaled corticosteroids (ICSs) have largely replaced oral corticosteroids (OCSs) in the management of severe persistent asthma, a substantial number of asthmatic subjects still use OCSs because they are perceived to be steroid dependent or they have recurrent exacerbations necessitating frequent bursts of OCSs. On the basis of pharmacy database information on a large asthmatic population, we found that approximately 4% of asthmatic subjects received OCSs for a minimum of 28 days or had at least 3 prescriptions for OCSs filled per year.¹ The actual prevalence of OCS use is probably higher, however, because the population studied was less than 44 years of age, and it is likely that a higher percentage of older asthmatic subjects take OCSs because of a greater prevalence of chronic persistent airway obstruction.²

Abbreviations used

AQLQ:	Asthma quality-of-life questionnaire
HPA:	Hypothalamic-pituitary-adrenal
HRQOL:	Health-related quality of life
ICS:	Inhaled corticosteroid
MF:	Mometasone furoate
OCS:	Oral corticosteroid
PEF:	Peak expiratory flow

Because of the adverse systemic effects of OCSs, there has been considerable interest in finding effective treatment alternatives for severe persistent asthma. As our knowledge of the inflammatory pathogenesis of asthma has evolved, various drugs used for other inflammatory disorders have been examined in terms of their antiasthmatic activity. Agents such as methotrexate, cyclosporine, and gold salts have been studied, and although some have had salutary effects, none have demonstrated a risk-benefit profile to justify their widespread use.³ Recent studies have shown the newer potent ICSs budesonide and fluticasone propionate to be effective in allowing complete elimination of OCSs in a significant number of OCS-dependent asthmatic subjects.⁴⁻⁶ The advantage of these agents derives from their high ratio of topical to systemic activity.⁷ Studies with dry powder formulations of both budesonide and fluticasone propionate have demonstrated that doses allowing complete elimination of OCSs produce less hypothalamic-pituitary-adrenal (HPA) axis suppression than 10 mg of prednisone.^{8,9}

Mometasone furoate (MF) is a potent topical glucocorticoid that has been available for several years in dermatologic and nasal formulations.¹⁰⁻¹³ In vitro studies indicate that MF and fluticasone propionate are of similar potency with respect to glucocorticoid receptor binding and transactivation of gene expression,¹⁴ as well as suppression of cytokine production from CD4⁺ T cells.^{15,16} Now formulated for oral inhalation as a powder-lactose agglomerate administered by means of a novel breath-actuated dry powder inhaler (Twisthaler), MF has been shown to be well tolerated and efficacious, whether administered once daily¹⁷ or twice daily,¹⁸ in patients with persistent asthma. Furthermore, MF at doses of 400 and 800 µg twice daily causes minimal adverse effects on the HPA axis relative to a 10-mg dose of prednisone.¹⁹

We examined the efficacy and safety of MF in a 3-month, randomized, controlled trial followed by a 9-month open-label study. The goal of this study was to determine whether MF was effective in reducing OCS requirements in steroid-dependent patients with severe persistent asthma. We report findings that indicate that MF is effective in reducing or eliminating OCS requirements in patients previously unable to be weaned from OCSs while taking other ICSs.

METHODS

Patients

Male and nonlactating female patients 12 years of age or older with OCS-dependent asthma were recruited from existing patient

populations and through advertising at each of 21 medical centers. For eligibility, patients were required to have had severe persistent asthma for at least 12 months before enrollment,²⁰ and they were required to have needed daily or alternate-day OCSs for asthma control for 5 or more of the 6 months before enrollment. Eligible patients were also required to have an FEV₁ of 40% to 85% of predicted value and documentation of a 12% or greater increase in FEV₁ with an absolute volume increase of 200 mL or greater in response to a β-agonist or glucocorticoid treatment within the previous 12 months. For each patient, the minimum effective prednisone dose was established. This was determined through source documents verifying that attempts at OCS dose reduction in the previous 6 months resulted in clinical deterioration or reduced lung function. If such documentation was not available, the investigator, before screening, imposed a stepwise reduction in prednisone dose until pulmonary function decreased. The patient was then returned to the previous dose step, thus establishing the minimum effective dose. Those stable on a minimum effective dose in the range of 5 to 30 mg daily or 10 to 60 mg every other day were eligible. Institutional review boards representing each center approved the protocol, and written informed consent was obtained from each patient before participation.

Protocol design

The study consisted of an initial 3-month, parallel, double-blind, randomized, placebo-controlled phase comparing MF (400 µg twice daily and 800 µg twice daily) with placebo, followed by a 9-month open-label treatment phase with all patients taking MF. All drugs were administered as a dry powder through a Twisthaler. Patients were enrolled in a 2-week run-in period before randomization during which the usual prescribed ICS and the minimum effective dose of prednisone were continued. At the end of the run-in period, the usual prescribed ICSs were discontinued, and patients were randomized to MF 400 µg twice daily, MF 800 µg twice daily, or placebo in place of their previously prescribed ICS. Patients taking theophylline, nebulized or oral β-agonists, salmeterol, cromolyn, nedocromil, or anticholinergics were to continue these throughout the study. Throughout the study, morning and evening peak expiratory flow (PEF), asthma symptoms, number of albuterol inhalations, adverse events, and medication use were documented on daily diary cards.

After randomization, visits occurred at day 4, week 1, and weekly thereafter until the double-blind treatment phase ended. Treatment failure as a result of asthma worsening occurred under the following conditions: (1) an asthma exacerbation leading to hospitalization; (2) an increase in any asthma medication except inhaled albuterol or prednisone to control symptoms; and (3) requirement for a third burst of prednisone to treat worsening symptoms. For patients with asthma exacerbations, a prednisone burst of 60 mg tapered over a 2-week period to a dose 2.5 mg above the pre-burst daily prednisone dosage was allowed. If a second prednisone burst was required, patients were maintained on a fixed prednisone dose for the remainder of the double-blind treatment phase. A third prednisone burst resulted in treatment failure, as noted above.

Patients completing the 12-week randomized treatment phase and those discontinuing because of treatment failure were eligible to be enrolled in the 9-month open-label phase. Visits were weekly for the first 4 visits and at 4-week intervals thereafter until the final visit at week 40. In the 9-month open-label phase, patients were initially given MF 800 µg twice daily, and the dose could be tapered to as low as 400 µg twice daily if the patient had completely eliminated prednisone for a period of 4 weeks. Patients requiring a prednisone burst during this phase had the MF dose increased to 800 µg twice daily, and further dose reductions were not attempted for at least 2 months after the prednisone burst.

Patients were evaluated at each visit to determine eligibility for prednisone dose reduction. The dose was reduced if the following

criteria were met: (1) $FEV_1 \pm 20\%$ of baseline and at least 40% of predicted value; (2) morning PEF $\pm 20\%$ of mean baseline; (3) albuterol use not greater than 4 puffs above baseline and a 50% or less increase in nocturnal awakenings compared with baseline; (4) prednisone burst not required in the preceding 7 days; and (5) 2 prednisone bursts not used since the last visit. For patients on a once-daily regimen, the dose was reduced in 5-mg steps between 30 and 10 mg, in 2.5 mg steps between 10 and 5 mg, and in 1.25 mg steps between 5 and 0 mg. A similar schedule was used for patients receiving alternate-day prednisone.

Efficacy measurements

The primary outcome measure was the percentage change in daily prednisone requirement from baseline to the end of the study for the double-blind treatment phase. Other outcome measures included spirometric measurements (FEV_1 ; forced vital capacity; and forced expiratory flow, midexpiratory phase), morning and evening PEF, rescue albuterol use, asthma symptom scores, number of nocturnal awakenings caused by asthma that required albuterol use, and general and asthma-specific quality-of-life measures. The highest FEV_1 from 3 measurements was analyzed. Spirometry was performed 2 hours after withholding albuterol. The PEF recorded was the highest of triplicate measurements made with a Personal Best peak flowmeter. Symptom severity for wheezing, difficulty breathing, and cough was rated by the patient on a 4-point scale (0 = none, 1 = noticeable, 2 = annoying, and 3 = very uncomfortable). For PEF and symptoms, the average value for the 7 days preceding the baseline visit and all subsequent weeks was analyzed. Quality of life was measured by using the acute form of the SF-36²¹ to determine health-related quality of life (HRQOL) and an asthma-specific quality-of-life questionnaire, the AQLQ.²² Using the previous week for reference, questionnaires were administered in the clinic at baseline and at endpoint of the double-blind treatment phase.

Plasma MF concentrations

Plasma samples taken at week 12 were analyzed at 10 centers for MF concentrations. High-pressure liquid chromatography with mass spectrometry was used to quantitate MF levels before and 30 minutes after dosing. The limit of detection was 50 pg/mL.

Safety assessments

Patients were monitored for adverse events, changes in physical findings, vital signs, hematologic and blood chemistry profiles, and electrocardiographic profiles. The investigator assessed the relationship of adverse events to use of study drug on the basis of temporal factors and the likelihood of other causes.

Statistical analysis

A sample size of 45 per treatment arm was chosen to detect, with 90% power and a 5% significance level, a clinically relevant ($\geq 40\%$) pairwise difference in the mean percentage change from baseline to endpoint in daily prednisone requirement between any active treatment group and the placebo group.⁴ Endpoint was defined as the last observation obtained for an individual during the treatment period. Analysis of the primary efficacy variable was based on all randomized patients who received at least one dose of study medication and who had postbaseline data (intent-to-treat principle). In addition to the endpoint analysis, pairwise comparisons among the 3 treatment groups (400 μ g twice daily to placebo; 800 μ g twice daily to placebo; 400 μ g twice daily to 800 μ g twice daily) were made with respect to the percentage change from baseline in daily prednisone for each scheduled visit. All other efficacy variables were analyzed at each time point. Both primary and secondary endpoints were analyzed by using a 2-way ANOVA. In addition, the baseline values of oral prednisone requirement for the 3 groups and

the consistency of results across centers were assessed. All values are reported as means $\pm$ SEM.

RESULTS

Patient characteristics

One hundred thirty-two patients were randomized. Demographic and baseline data were similar among groups (Table I). Most patients (87%) were taking ICSs at the time of enrollment, and the distribution of different formulations and doses was comparable among groups.

Double-blind treatment phase

Of randomized patients, 95 (72%) completed the double-blind treatment phase. Twenty-three (55%) patients taking placebo discontinued before 3 months because of treatment failure (worsened asthma), whereas only 3 (7%) patients receiving MF 400 μ g twice daily and 5 (12%) patients receiving MF 800 μ g twice daily discontinued because of treatment failure. One patient in the 400- μ g group was lost to follow-up after the initial randomization visit and was not included in the analyses. Others discontinued but included in the analysis included 2 patients who were discontinued because of lack of compliance with the protocol and 3 patients who were discontinued because of adverse events unrelated to asthma (see "Safety assessment"). Kaplan-Meier analysis of the probability of remaining in the study (ie, time to treatment failure because of worsening asthma) revealed significant differences between both active treatment groups and the placebo group (Fig 1).

Oral prednisone use. At study endpoint, prednisone doses (primary endpoint) decreased -46.0% and -23.9% relative to baseline in the MF 400- μ g twice daily and MF 800- μ g twice daily groups, respectively. This compared with a 164.4% increase in the placebo group ($P < .01$, Fig 2). Eighteen (40%) patients in the MF 400- μ g twice daily group and 16 (37%) patients in the MF 800- μ g twice daily group were able to discontinue prednisone altogether compared with none in the placebo group. Furthermore, 62% and 60% of patients receiving MF 400 μ g twice daily and MF 800 μ g twice daily, respectively, decreased their prednisone dose by 50% or greater compared with only 7% of the placebo group. In fact, 60% of patients receiving placebo increased their daily prednisone use (Fig 3). Demographics of the 34 patients eliminating OCSs were reviewed, and there were no relationships identified between eliminating OCSs and age, sex, duration of asthma, and dose or type of ICS used before the study.

Pulmonary function. Compared with placebo, active treatment produced significant increases in pulmonary function (Table II and Fig 4). Moreover, within-group comparisons revealed that FEV_1 and morning PEF were significantly improved between baseline and endpoint in both active treatment groups despite reduced prednisone use (Table II). The FEV_1 decline between baseline and endpoint in the placebo group was also significant but not unexpected because of discontinuation of ICSs at randomization.

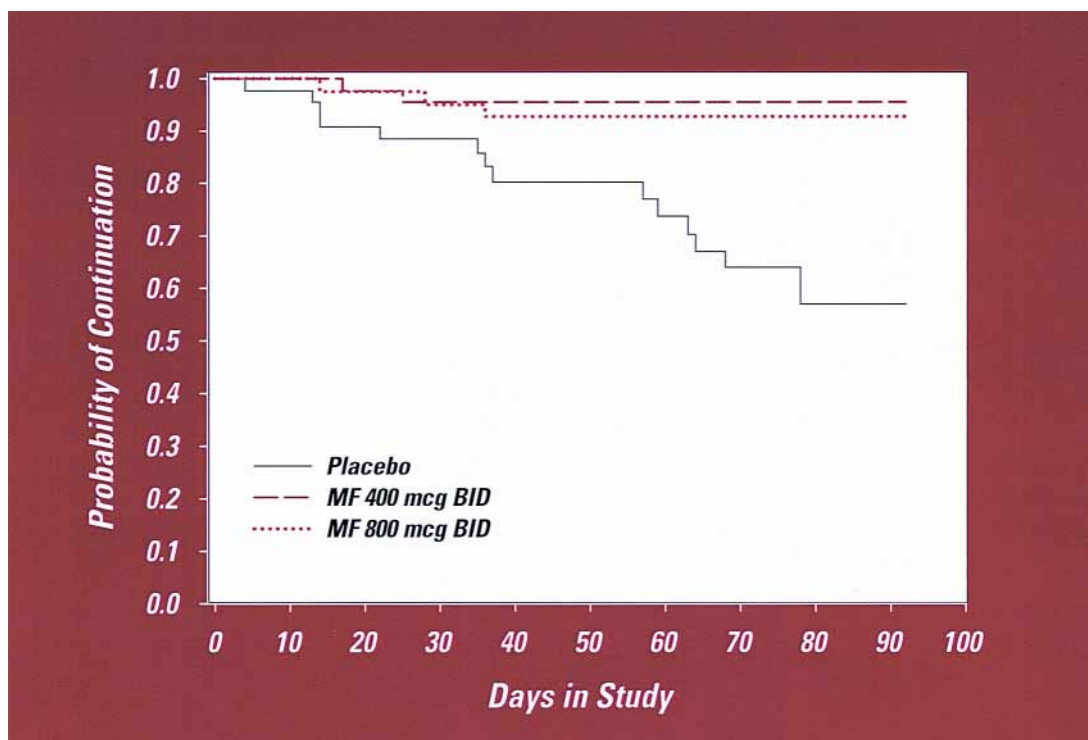


FIG 1. Kaplan-Meier estimates of time to asthma worsening (treatment failure). Both MF dry powder inhaler treatment groups had a greater probability of remaining in the study compared with the placebo group ($P < .01$). *BID*, Twice daily.

TABLE I. Summary of demographics and asthma-related characteristics for all patients

	Placebo	MF-DPI 400 µg BID	MF-DPI 800 µg BID
Demographics			
No. of patients	43	46*	43
Sex (M/F)	24/19	22/24	16/27
White/African American/other	37/3/3	35/8/3	39/3/1
Mean age, y (range)	55 (26-79)	49 (13-83)	53 (22-77)
Body weight, lb (range)	184 (132-282)	182 (120-275)	185 (120-286)
Never smoked/not in 6 mo	23/20	29/17†	30/13
Asthma-related characteristics (mean [range])			
Mean duration of asthma, y	23 (2-69)	21 (2-51)	19 (1-51)
FEV ₁ , % predicted	57 (26-85)	59 (40-84)	61 (38-91)
Prestudy therapy			
Prednisone regimen (% daily)	84	74	85
Inhaled glucocorticosteroids, n (mean µg/d)			
Beclomethasone dipropionate	4 (410)	7 (444)	5 (454)
Budesonide	0	0	3 (1067)
Flunisolide	7 (1076)	8 (1750)	5 (1300)
Fluticasone propionate	15 (666)	12 (770)	9 (953)
Triamcinolone acetonide	15 (1253)	15 (987)	10 (1130)
Theophylline use, n	21	25	26
Salmeterol use, n	23	30	21

DPI, Dry powder inhaler; *BID*, twice daily.

*One patient was lost to follow-up after the baseline visit, reducing patient number to 45 in Table II.

†One patient had smoked within the last 6 months.

Symptoms and rescue medication use. Symptom scores and nocturnal awakenings were significantly improved with both MF doses compared with placebo (Table II). Nocturnal awakenings fell 57% and 66%, respectively, in the MF 400 µg twice daily and MF 800

µg twice daily groups and increased by 62% in the placebo group ($P < .01$). Compared with placebo, daily rescue albuterol use was significantly reduced in the MF 400 µg twice daily group but not in the MF 800 µg twice daily group. Within-group analysis demonstrated that reduced

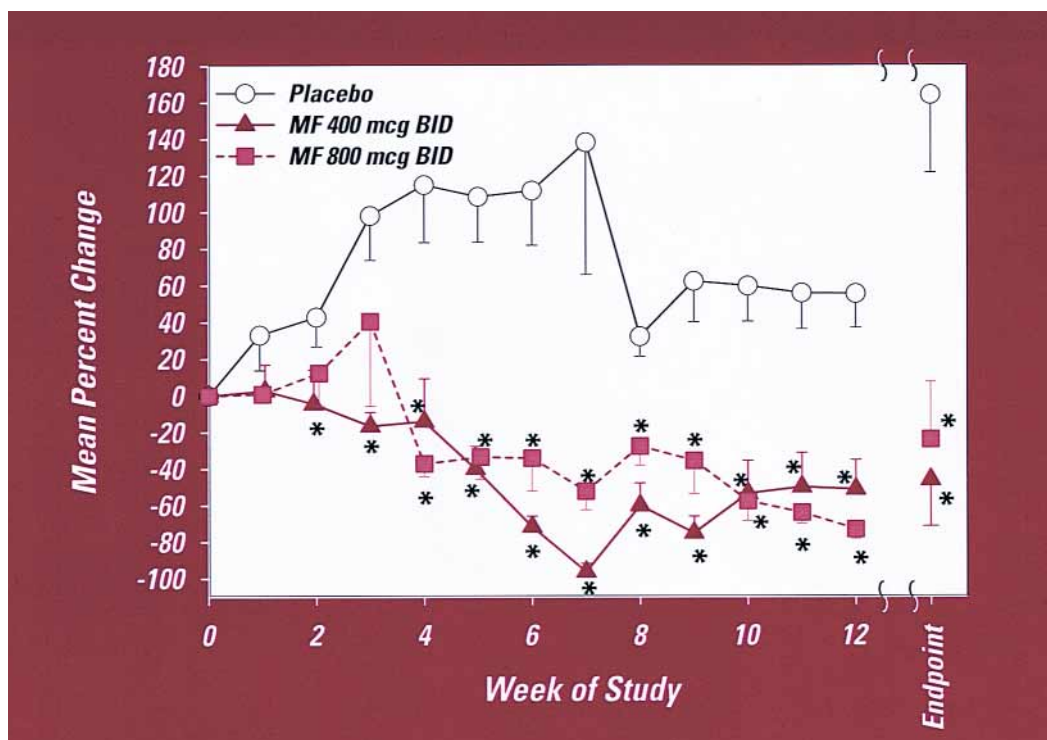


FIG 2. Effects of MF dry powder inhaler on prednisone use. The means of the individual percentage changes are shown over 12 weeks and at endpoint. Asterisks indicate values that are significantly different from those of the placebo group ($P < .05$). BID, Twice daily.

albuterol use in the MF 400 μ g twice daily group was also significantly different from baseline ($P < .01$).

Quality-of-life measures. SF-36 scores at baseline for all groups indicated that this population had a significant decrement in functional status compared with a general population sample.²¹ Decrements were recorded in physical functioning (54.5 ± 2.0 vs 84.2 ± 0.5 [mean $\pm$ SEM]), role limitation because of physical health problems (55.3 ± 3.6 vs 81.0 ± 0.7), general perception of health (51.5 ± 1.9 vs 72.0 ± 0.4), and vitality (52.0 ± 1.7 vs 60.9 ± 0.4). Scores for social functioning (77.1 ± 1.9), bodily pain (71.2 ± 2.0), role limitation because of emotional health problems (74.5 ± 3.3), and mental health (74.0 ± 1.6) did not differ greatly from values for the general population of 83.3 ± 0.5 , 75.2 ± 0.5 , 81.3 ± 0.7 , and 74.7 ± 0.4 , respectively.²¹ The effect of asthma on quality of life in the study population was seen also in baseline scores for the AQLQ questionnaire (data not shown). Patients described the effect of their asthma during the past week as moderate to severe, with the greatest effect in domains of breathlessness, social effect, and asthma concerns.

At the double-blind treatment phase endpoint, patients on active treatment had HRQOL scores similar to or, in the case of physical functioning, improved from those at baseline. Compared with placebo-treated patients who recorded deterioration from baseline, those on active treatment had significantly better scores ($P < .05$) in the physical component summary (a weighted average of the 8 SF-36 domains),²¹ as well as a clinically and statistically significant improvement in physical functioning (P

$< .01$). When summarized separately, those receiving either dose of MF who completely eliminated prednisone had HRQOL scores that tended to approach those of the general population (ie, physical functioning, 75.6 ± 3.7 ; role physical, 72.7 ± 6.9 ; general health, 67.5 ± 3.1 ; and vitality, 60.8 ± 3.1).

AQLQ scores revealed deterioration in the placebo group across all domains (ie, breathlessness, mood, social effect, asthma concerns, physical symptoms, and psychosocial effect). By contrast, clinically significant improvements from baseline were noted in both MF-treated groups in breathlessness, social effect, and asthma concerns, and scores for all domains were significantly better in the MF groups compared with those in the placebo group ($P < .05$).

Open-label phase

Of 128 patients entering the 9-month open-label phase, all received at least one dose of MF. One patient did not have efficacy data. Of these, 106 (83%) completed this phase, whereas 2 patients were discontinued for adverse events, 9 had asthma-related treatment failures, 3 did not wish to continue, and 8 were discontinued for noncompliance.

At endpoint of the open-label phase, there was an overall 54.1% reduction in prednisone dose compared with that at baseline before randomization. For those receiving placebo, MF 400 μ g twice daily, and MF 800 μ g twice daily during double-blind treatment, prednisone was reduced at endpoint by 61.6%, 58.1%, and 42.5%,

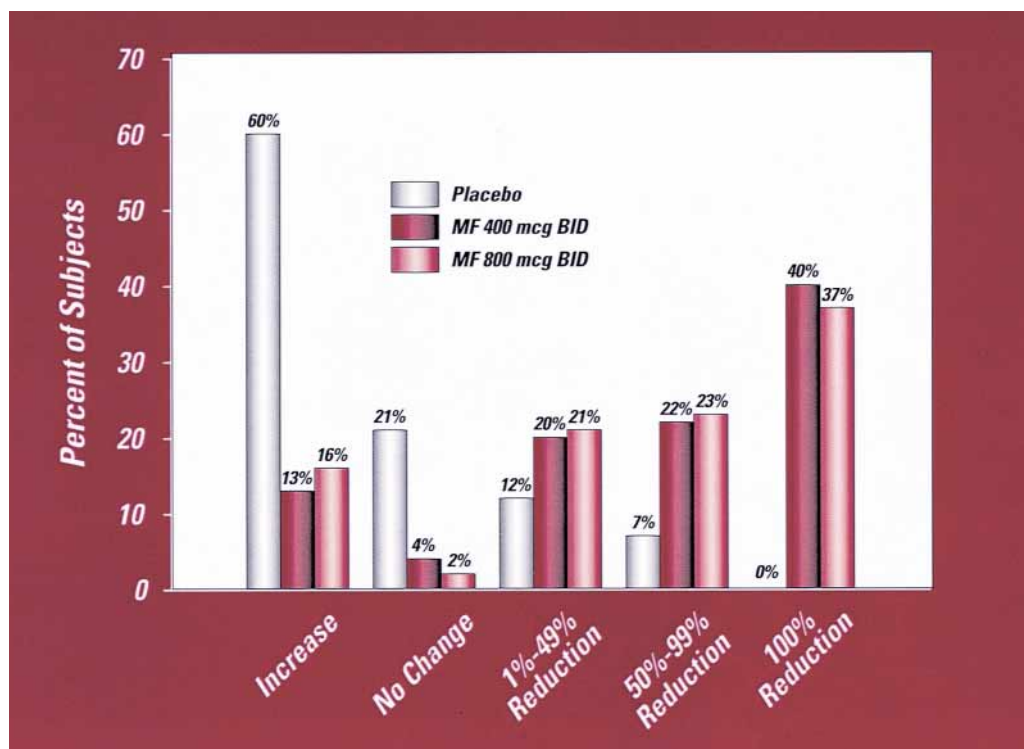


FIG 3. The distribution of prednisone dose reduction from baseline to endpoint. BID, Twice daily.

respectively. The endpoint measurement included patients discontinuing the study for any reason. From the time of randomization to the endpoint of the 9-month open-label phase, 64% of 127 patients completely eliminated prednisone. Prednisone was completely eliminated by 58%, 71%, and 62%, respectively, for groups receiving placebo, MF 400 μ g twice daily, and MF 800 μ g twice daily during the double-blind phase. Of the 95 patients who completed the entire 12 months of the study with evaluable data at the final week 52 visit, 76% completely eliminated oral prednisone. A substantial portion of patients (31%) decreased the dose of MF from 800 to 400 μ g twice daily.

Safety assessment

Double-blind treatment phase. MF was well tolerated, and no unusual or unexpected adverse events were reported. Most adverse events, including those related to treatment, were mild to moderate in severity, and none were life threatening. Treatment-related oral candidiasis was observed in 20% and 23% of patients in the MF 400- μ g and 800- μ g groups, respectively, and in 9% of the placebo group, none of whom discontinued treatment. Dysphonia was reported by 7% and 12% of patients receiving MF 400 μ g and 800 μ g, respectively, and in none of the placebo group. Adverse events related to prednisone withdrawal (eg, musculoskeletal pain, fatigue, and depression) were reported by 46% of patients receiving MF 400- μ g twice daily, 33% of patients receiving 800- μ g twice daily, and 16% of patients receiving placebo.

Three patients were discontinued from the study because of adverse events unrelated to treatment and unrelated to asthma worsening. Two patients were hospitalized for asthma exacerbations during the double-blind treatment phase, both in the MF 400- μ g twice daily group. No clinically meaningful changes were observed in clinical laboratory tests, electrocardiograms, or vital signs.

Open-label phase. There was no indication of an increase in incidence of clinically meaningful adverse events with prolonged treatment. Oral candidiasis and dysphonia were the most frequently reported treatment-related adverse events, occurring in 37% of patients, none of whom discontinued treatment.

Two patients discontinued because of adverse events unrelated to treatment, one with aggravated asthma and one with a breast neoplasm. Seven patients were hospitalized for asthma exacerbations; one was hospitalized on 5 occasions. There were no clinically relevant changes in electrocardiograms or clinical laboratory tests.

DISCUSSION

We found a clinically significant OCS-sparing effect of MF administered by means of a dry powder inhaler. Compared with patients receiving placebo whose prednisone requirements increased after randomization, those receiving either dose of MF were able to significantly reduce their prednisone requirements, and a substantial proportion discontinued its use altogether. Coincident with prednisone reduction, MF-treated patients experi-

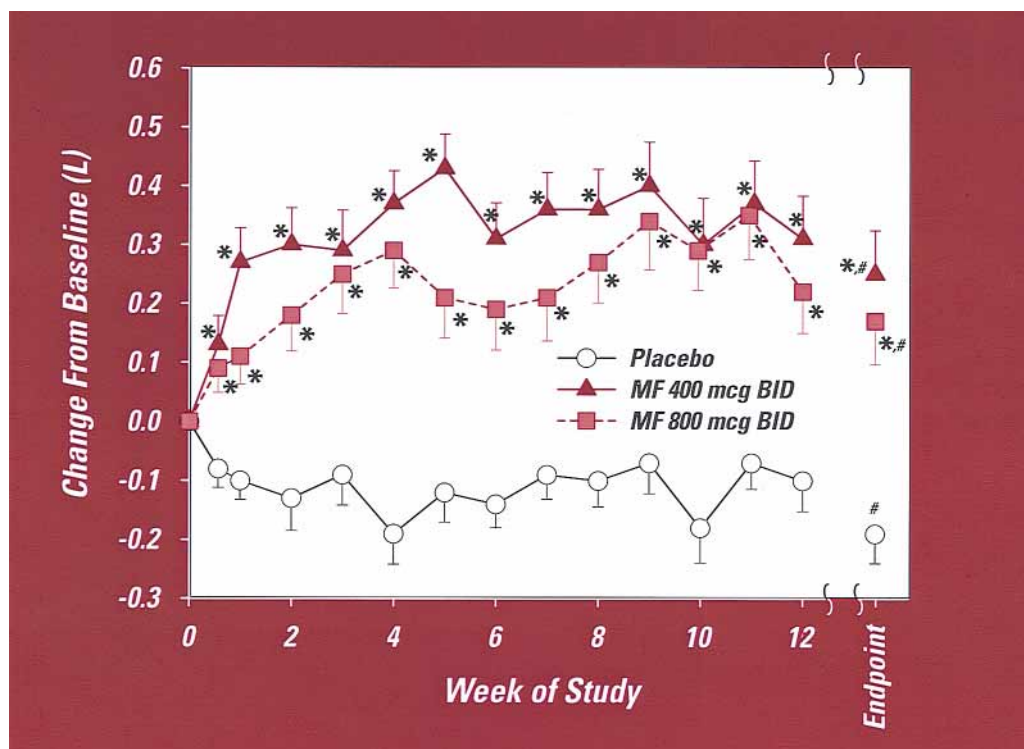


FIG 4. Effects of MF dry powder inhaler on mean change in FEV₁ from baseline are shown over 12 weeks and at endpoint. Asterisks indicate values that are significantly different from those of the placebo group ($P < .05$). Number signs indicate values at endpoint that are significantly different from those at baseline ($P < .05$). BID, Twice daily.

enced significantly better pulmonary function and symptom scores, significantly less rescue albuterol use, and better quality of life.

Because the ICSs taken at baseline were discontinued at randomization, deterioration in the placebo group during double-blind treatment was not unexpected. The observation is nevertheless important because this deterioration is evidence that the study population indeed had OCS-dependent asthma. It is important to note that differences between active treatment and placebo groups are not simply related to deterioration in the placebo group. Post hoc analysis of within-group changes in FEV₁, morning PEF, and rescue albuterol use revealed that for the MF treatment groups, improvements between baseline and endpoint of double-blind treatment were significant.

The improvements from baseline in lung function and rescue albuterol use in the MF treatment groups are notable because they occurred in the face of a 46.0% and 23.9% decline in prednisone use in the 400- μ g twice daily and 800- μ g twice daily groups, respectively. Lung function deterioration in the placebo group is also notable because it occurred despite a substantial increase in prednisone use. These findings suggest that ICSs may provide salutary effects that are not achieved with systemic corticosteroids. Further studies comparing MF with other ICSs are needed to explore whether MF offers any unique advantages over other compounds.

The steroid-sparing effects of MF are further illustrated by the finding that prednisone use was completely

eliminated in 40% of patients taking MF 400 μ g twice daily within the first 12 weeks of the study and in 64% within 1 year. Similar steroid-sparing effects have recently been reported with other ICSs.⁴⁻⁶ Nelson et al⁵ reported that among patients taking budesonide 400 μ g twice daily or 800 μ g twice daily administered by means of a Turbuhaler for 20 weeks, respectively, there was a 68% and 64% rate of complete OCS elimination. Nelson et al⁶ also reported complete elimination of OCSs in 75% and 89% of patients taking fluticasone propionate 500 μ g twice daily or 1000 μ g twice daily in a dry powder formulation for 16 weeks, respectively. Using fluticasone propionate administered by means of a metered-dose inhaler for 16 weeks, Noonan et al⁴ found an 88% elimination of OCSs at 1000 μ g twice daily and a 69% elimination at 750 μ g twice daily.

Several important differences between the present study and those cited above preclude meaningful comparisons of outcomes. First, the present study differs from earlier studies in strictly enforcing the titration of OCS doses to the minimum effective dose needed to maintain control before entry. This was done to ensure that the study population was truly steroid dependent. In fact, not a single patient receiving placebo could completely eliminate prednisone. This is in contrast to earlier studies in which 3% to 9% of patients receiving placebo successfully completely eliminated OCSs.⁴⁻⁶ Second, the double-blind phase of the present study was 12 weeks in duration, as opposed to the longer duration (16-20 weeks) in previ-

TABLE II. Summary of baseline and change at endpoint data from the double-blind phase for parameters monitored for all patients enrolled

	Placebo (n = 43)	MF-DPI 400 µg BID	MF-DPI 800 µg BID
Daily oral prednisone dose (mg)			
Baseline	11.56	11.93	12.02
Change	+11.81	-6.33*	-3.19*
Pulmonary function			
FEV ₁ (L)			
Baseline	1.78 ± 0.09	1.87 ± 0.09	1.79 ± 0.08
Change	-0.19 ± 0.05	+0.25 ± 0.07†	+0.17 ± 0.07†
FVC (L)			
Baseline	2.89 ± 0.12	2.93 ± 0.13	2.86 ± 0.14
Change	-0.18 ± 0.11	+0.18 ± 0.10*	+0.13 ± 0.09*
FEF _{25%-75%} (L/s)			
Baseline	1.10 ± 0.10	1.21 ± 0.10	1.18 ± 0.09
Change	-0.14 ± 0.05	+0.33 ± 0.09†	+0.23 ± 0.09†
Morning PEF rate (L/min)			
Baseline	316 ± 16	324 ± 14	299 ± 15
Change	-37.51 ± 7.19	+40.97 ± 9.56†	+42.21 ± 13.21†
Patient self-reports			
Morning wheezing score			
Baseline	0.70	0.79	0.56
Change	+0.35	-0.31†	-0.19†
Morning difficulty breathing score			
Baseline	0.76	0.82	0.72
Change	+0.42	-0.33†	-0.16†
Morning cough score			
Baseline	0.50	0.49	0.43
Change	+0.30	-0.07*	-0.09*
Albuterol use (inhalations/d)			
Baseline	5.10	4.97	4.21
Change	+0.29	-1.83†	-0.88
Nocturnal awakenings (per night)			
Baseline	0.29	0.53†	0.44*
Change	+0.18	-0.30†	-0.29†

Mean values (± SEM for pulmonary function) are indicated for each group. One patient in the MF dry powder inhaler 400-µg twice daily group was lost to follow-up after the baseline visit.

DPI, Dry powder inhaler; BID, twice daily; FVC, forced vital capacity; FEF_{25%-75%}, forced expiratory flow, midexpiratory phase.

**P* < .05 versus placebo.

†*P* < .01 versus placebo.

ous studies.⁴⁻⁶ The open-label phase of the study demonstrates that a longer duration of treatment with MF was efficacious in further reducing prednisone requirements.

We obtained comparable results with either the 400-µg twice daily or the 800-µg twice daily dose, suggesting that for this population of patients with severe steroid-dependent asthma, the 400-µg twice daily dose is at or near the peak of its efficacy dose-response relationship. The difficulties in demonstrating dose-response relationships with inhaled steroids in patients with less severe asthma are well known,^{23,24} although dose-related effects have been demonstrated under conditions in which asthma deterioration was induced by removing and then replacing ICSs.²⁵ Other investigators have reported dose-response relationships in reducing oral prednisone requirements by using fluticasone propionate and have suggested that such relationships are more likely to be found in subjects with severe asthma.^{4,6} On the other hand, dose-related effects could not be established between 400-µg twice daily and 800-µg twice daily

doses of budesonide in a similar OCS-sparing study.⁵ Because we did not examine the effects of lower doses in this population, we are uncertain whether lower doses would be equally effective or provide less benefit. On the basis of the present study, however, we would recommend use of the lower 400-µg twice daily dose so as to limit systemic exposure and potential toxicity. A study of MF in patients with mild persistent asthma has shown that after 28 days of treatment with 400 µg twice daily and 800 µg twice daily, there is, respectively, a 10% and 21% suppression of the plasma cortisol levels (24-hour area under the curve) compared with a 64% suppression with a daily dose of 10 mg of prednisone.¹⁹

The major shortcoming of this study was a lack of data analyzing HPA axis function. Changes in plasma cortisol concentration after Cortrosyn stimulation were measured at screening and at the endpoints of the double-blind and open-label phases at 10 selected centers. However, because the assay used to measure cortisol cross-reacted with prednisolone, a prednisone metabolite, the data

could not be interpreted. Previous studies with budesonide 1600 µg and fluticasone propionate 2000 µg revealed trends toward improved adrenal function in patients whose OCSs were reduced or eliminated.^{5,6} Given these findings and the observation that MF at the doses used in this study had less HPA axis suppression than a 10-mg daily dose of prednisone,¹⁹ it is unlikely that adrenal function would have worsened on active treatment during the course of this study. The measurements of plasma MF concentrations in this study indicated minimal systemic exposure to MF. At a dose of 400 µg twice daily, plasma concentrations of MF were low and close to the limit of detection. Furthermore, MF concentrations were not detectable in all patients.

Both doses of MF were well tolerated. The most commonly reported adverse events were related to prednisone withdrawal, an expected complication. The most common adverse events related to MF were oral candidiasis and dysphonia, and the frequency of these events was in the range reported for other ICSs in similar studies.⁴⁻⁶ There was no indication of an increase in frequency of adverse events with long-term treatment with MF.

Because of the well-known adverse systemic effects of OCSs, there is a need for more effective and safer treatment alternatives for patients with severe persistent asthma. On the basis of the results reported here, we conclude that MF 400 µg twice daily given as an inhaled dry powder is a safe and effective alternative to OCSs in patients with severe persistent asthma.

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