

Effects of Mometasone, Fluticasone, and Montelukast on Bone Mineral Density in Adults with Asthma

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What is already known about this topic? Investigations in the published literature have shown reduction in bone mineral density after chronic exposure to a range of inhaled corticosteroid formulations and delivery devices.

What does this article add to our knowledge? This report provides new information on bone safety from a study of inhaled mometasone furoate compared with montelukast and fluticasone propionate in men and women with asthma.

How does this study impact current management guidelines? This study provides evidence of bone safety after 1 year of treatment with inhaled mometasone furoate, which reinforces the National Heart, Lung, and Blood Institute Expert Panel conclusion that inhaled corticosteroids are well tolerated and safe at the recommended dosages.

BACKGROUND: Associations of inhaled corticosteroids (ICS) with bone mineral density (BMD) loss have not been characterized consistently.

OBJECTIVE: This randomized, double-blind study assessed effects of mometasone furoate (MF) administered via dry powder inhaler on BMD of patients with persistent asthma.

METHODS: Adults with mild-moderate persistent asthma who did not receive ICS for ≥ 3 months were randomized to MF 400 μg once daily (QD) in the evening (PM), MF 200 μg QD PM,

montelukast sodium (ML) 10 mg QD PM, or fluticasone propionate (FP) 250 μg twice daily. Included patients had 25-hydroxy vitamin D levels ≥ 15 ng/mL at baseline. All the patients received calcium and vitamin D supplements for daily use during the trial. Duplicate BMD scans were done at baseline, 6 months, and 1 year. The mean percentage change in lumbar spine (LS) BMD from baseline to end point for MF 400 μg versus ML 10 mg was the primary analysis. Changes from baseline in left total femur BMD and femoral neck BMD were secondary assessments.

RESULTS: At the end point, mean LS BMD increased 0.9% (MF 400 μg), 1.2% (ML), 0.7% (MF 200 μg), and 1.1% (FP), with no significant differences for MF 400 μg versus ML (-0.3% [95% CI, -1.01 to 0.27]) for LS BMD. No significant differences among treatments occurred for changes in left total femur BMD; all were slight increases. Changes in femoral neck BMD were 0.4% (MF 400 μg), -0.2% (ML), -0.2% (MF 200 μg), and -0.4% (FP); only the difference between MF 400 μg and FP was statistically significant ($P = .044$).

CONCLUSION: No detrimental effects on lumbar BMD were observed after up to 1 year of treatment with MF in comparison with ML for patients who received calcium and vitamin D supplements. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2013;1:649-55)

Key words: Bone mineral density; Lumbar spine; Inhaled corticosteroids; Asthma

Inhaled corticosteroid (ICS) is a foundation of asthma management and are the only maintenance medications that reduce asthma-related death.¹⁻³ There is evidence to indicate that patients with asthma that requires ICS therapy may be at risk for reduced bone mineral density (BMD).⁴⁻⁹ These effects on BMD appear to associate with chronic use and consequent exposure to an increasing cumulative dose.^{5,10} Reduced BMD is a risk factor for fracture, particularly among older individuals, with substantial implications for health care utilization and morbidity.¹¹ The intersection of an aging population with the potential

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*H. Staudinger and A. Teper were employed by Merck & Co Inc when this manuscript was submitted and revised.

This study was funded by Merck & Co Inc, Whitehouse Station, NJ.

Conflicts of interest: J. Maspero has received research or speaker grant support and/or honoraria from and/or has served as an advisory board member, consultant, and/or speaker for Allergy Therapeutics, AstraZeneca, GlaxoSmithKline, Merck & Co Inc., and Uriach; has received a grant from Fundación Cidea; is a board member for Merck & Co Inc; and has received payment for lectures from Merck, GlaxoSmithKline, and Allergy Therapeutics. V. Backer has received unrestricted grants from and/or has served as an advisory board member, consultant, and/or speaker (earlier or currently) or AstraZeneca, GlaxoSmithKline, Merck, Novartis, Boehringer Ingelheim, Pharmaxis, Nigard, Maribo Medico, Norpharma, Cheisi, ALK-Abelló, and TEVA. A. Teper and H. Staudinger were employed by Merck & Co Inc, and as such received travel support and stock/stock options from Merck & Co Inc. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication September 14, 2012; revised July 17, 2013; accepted for publication July 30, 2013.

Available online October 10, 2013.

Cite this article as: Maspero J, Backer V, Yao R, Staudinger H, Teper A. Effects of mometasone, fluticasone, and montelukast on bone mineral density in adults with asthma. J Allergy Clin Immunol Pract 2013;1:649-55. <http://dx.doi.org/10.1016/j.jaip.2013.07.011>.

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2213-2198/\$36.00

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<http://dx.doi.org/10.1016/j.jaip.2013.07.011>

Abbreviations used

<i>AE</i> - Adverse event
<i>BID</i> - Twice daily
<i>BMD</i> - Bone mineral density
<i>DPI</i> - Dry powder inhaler
<i>FEF_{25%-75%}</i> - Forced expiratory flow at 25% to 75% of vital capacity
<i>FEV₁</i> - Forced expiratory volume in 1 second
<i>FP</i> - Fluticasone propionate
<i>FVC</i> - Forced vital capacity
<i>ICS</i> - Inhaled corticosteroid
<i>LABA</i> - Long-acting β_2 -agonist
<i>LS</i> - Lumbar spine
<i>LSM</i> - Least squares mean
<i>MDI</i> - Metered-dose inhaler
<i>MF</i> - Mometasone furoate
<i>ML</i> - Montelukast sodium
<i>PSD</i> - Pooled standard deviation
<i>QD</i> - Once daily
<i>SD</i> - Standard deviation

requirement for long-term ICS therapy mandates careful consideration of the treatment effects of these medications.

Investigating the effects of ICS treatment on BMD presents numerous methodologic challenges.¹² Patients in some ICS studies may have previously received short- or long-term therapy with oral corticosteroids, which have much more potent and well-established effects on bone structure. In addition, older patients, perimenopausal patients, patients with sedentary or another altered lifestyle secondary to intractable asthma, or another comorbidity may demonstrate decreased BMD through noncorticosteroid mechanisms, and a causal link between bone abnormalities and the ICS may be difficult to confirm.¹³ Although all currently marketed ICS may exhibit systemic effects at high doses, the systemic risks of long-term therapy with lower doses have not been completely characterized. Furthermore, the precise risk for BMD loss associated with different ICS and delivery systems may vary.⁵

Mometasone furoate (MF) delivered via a dry powder inhaler (DPI) is a synthetic corticosteroid approved for management of persistent asthma in patients aged >4 years. Current prescribing recommendations are that MF DPI therapy should be initiated at 200 μ g or 400 μ g given once daily (QD) in the evening (PM).¹⁴ Although previous trials evaluated MF DPI administered twice daily (BID),¹⁴ the effect of MF DPI administered QD in the evening on BMD has never been evaluated. We report findings from a phase IV, randomized, double-blind, 1-year study that compared the effects of MF DPI with the effects of montelukast sodium (ML) delivered by oral film-coated tablet, a leukotriene antagonist, and fluticasone propionate (FP) on BMD for female and male patients with mild-moderate persistent asthma.

METHODS

Study design and patients

This was a randomized, multicenter, double-blind, active-controlled, parallel-group, 52-week trial (ClinicalTrials.gov Identifier: NCT00394355) that evaluated the effects on BMD of MF DPI, oral ML, and FP administered by a metered-dose inhaler (MDI) in adults with asthma. ML is a guideline-recommended asthma-control medication that has no known

TABLE I. Summary of selected study methods

Exclusion criteria
Conditions that precluded normal ambulation or predisposed to immobility
Screening LS scans more than 2 SD below young normal
Significant pre-existing respiratory tract disease
Asthma that required systemic oral corticosteroid treatment
Severe asthma that required ≥ 12 inhalations of albuterol on any 2 consecutive days between screening and study entry
Asthma-related hospitalization in the past 3 mo
Any history of respiratory failure secondary to asthma that requires mechanical ventilation
Active tobacco users
Ex-smokers who had smoked within the past year
Patients with a history of pipe or cigar smoking
Ex-smokers with a cumulative smoking history of more than 10 pack years
The presence of any clinically significant disease other than asthma
Conditions known to adversely affect bone mineral metabolism
Clinically relevant conditions that could interfere with accurate bone densitometry
Recent exposure to immunosuppressive medications or medications known to interfere with bone metabolism (such as bisphosphonates)
BMD assessments
Participants who discontinued treatment before 52 weeks remained under follow-up through the study end point to continue BMD surveillance
Acceptable duplicate scans were technically satisfactory, without artifact, and were prespecified to agree within 5%, or a third scan was performed on the same day to resolve any disparities
Serum cortisol assessments
Blood samples were obtained at 11 prespecified time points at 1-, 2-, and 4-h intervals over a single 24-h period
Efficacy assessments
Spirometric measurements of lung function and assessment of patient-centered outcomes (eg, nocturnal awakenings, rescue bronchodilator use) were performed to evaluate clinically meaningful exposure to study treatment in all treatment groups over the course of the study
Statistical analysis
If the size of a BMD scan center was insufficient (ie, fewer than 4 patients total) for verification of interaction between BMD scan center and treatment, then such centers were pooled with the next smallest BMD scan center for the BMD analyses and interaction modeling

effects on BMD and functioned as a negative control. FP is a potent ICS prescribed worldwide for asthma therapy.

Patients provided informed written consent and were enrolled between October 2006 and November 2009 at 50 participating centers in Europe, North America, Central America, South America, and the Caribbean. Adult patients (women aged 18-40 years, men aged 18-50 years) were eligible for enrollment if they had at least a 3-month history of asthma and had not taken an ICS within the previous 3 months. All the patients demonstrated a prebronchodilator forced expiratory volume in 1 second $\geq 60\%$ and $\leq 90\%$ of predicted at entry. The patients were required to have 2 technically acceptable dual energy x-ray absorptiometry scans of the lumbar spine (LS), left total femur, and femoral neck that agreed within 5% and a 25-hydroxy vitamin D level ≥ 15 ng/mL before randomization. The patients were not randomized if they had low vitamin D levels or met other exclusion criteria (Table I).

TABLE II. Summary of demographics and disease characteristics (all randomized patients)

	MF DPI 400 µg QD PM (n = 137)	MF DPI 200 µg QD PM (n = 140)	FP MDI 250 µg BID (n = 147)	ML 10 mg QD PM (n = 142)
Sex, no. (%)				
Women	90 (66)	91 (65)	90 (61)	88 (62)
Men	47 (34)	49 (35)	57 (39)	54 (38)
Race, no. (%)				
White	36 (26)	35 (25)	38 (26)	34 (24)
Non-white	101 (74)	105 (75)	109 (74)	108 (76)
Asian	0	1 (1)	0	0
Black	0	0	0	1 (1)
Multiracial	101 (74)	104 (74)	109 (74)	107 (75)
Age, mean (SD)				
Women ≤40 y	28.4 ± 6.9	28.2 ± 7.3	27.3 ± 6.4	27.5 ± 6.0
Men ≤50 y	31.8 ± 9.5	32.6 ± 7.9	29.7 ± 7.6	29.5 ± 8.6
Height (cm), mean (SD)	163.4 ± 8.7	163.3 ± 9.2	162.83 ± 9.47	162.85 ± 9.37
Duration of asthma (y), mean (SD)	15.5 ± 10.00	14.0 ± 9.82	14.1 ± 9.94	14.4 ± 9.25
No. previous controller medication				
ICS alone	6	5	6	8
ICS/LABA	1	2	0	2
FEV ₁ (L), mean (SD)*	2.66 ± 0.55	2.60 ± 0.58	2.65 ± 0.53	2.70 ± 0.51
FEV ₁ , % predicted, mean (SD)*	76.51 ± 9.63	74.72 ± 9.21	75.31 ± 9.39	76.87 ± 9.26
Spinal BMD (g/cm ²), mean (SD),	1.08 (0.14)	1.10 (0.14)	1.10 (0.13)	1.09 (0.13)
T-score for spinal BMD	−0.31 (0.94)	−0.21 (0.98)	−0.19 (0.93)	−0.28 (0.94)

BMD, bone mineral density; FEV₁, Forced expiratory volume in 1 s; FP, fluticasone propionate delivered via metered dose inhaler; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; MF-DPI, mometasone furoate delivered via dry powder inhaler; ML, montelukast sodium delivered by oral film-coated tablet; QD PM, once daily in the evening; SD, standard deviation.

*At randomization.

The patients were randomized in a 2:2:2:1:1 ratio to 1 of 5 double-blinded treatments: MF DPI 200 µg QD PM plus ML placebo QD, MF DPI 400 µg QD PM plus ML placebo QD, FP MDI 250 µg BID plus ML placebo QD, ML 10 mg QD PM plus placebo DPI, or ML 10 mg QD PM plus placebo MDI. Randomization was centrally administered by using an interactive voice response system. In addition to the study treatment, all the participants received a calcium and vitamin D supplement (500 mg calcium plus 400 IU vitamin D) at screening for daily use during the study to minimize confounding effects of clinically significant calcium and vitamin D deficiency on BMD.

Assessments

The treatment duration was 52 weeks. The patients were regularly assessed during scheduled office visits at baseline (day 1) and weeks 1, 12, 26, 39, and 52, or via telephone call follow-up. Changes in BMD were assessed by duplicate dual energy x-ray absorptiometry scans of the LS (defined as L1-L4), the left total femur, and the femoral neck at week 26 and end point (Table I). All study scans were reviewed for quality assurance by a central dual energy x-ray absorptiometry center. Spirometry was performed at all visits to evaluate response to therapy and to confirm clinically meaningful exposure to study drugs (Table I). Rescue medication use and symptom scores were documented, and the patients were examined at all visits to evaluate for the presence of wheezing. Clinical laboratory tests were obtained, and adverse events (AE) were recorded. Blood samples for a 24-hour serum cortisol level were obtained at entry and week 52 at selected sites (Table I).

This was primarily a safety study. The primary outcome measurement was the mean percentage change in LS BMD from

baseline to end point for MF DPI 400 µg versus ML 10 mg. The end point was the last postbaseline nonmissing scan result. Patients with a ≥6% decrease in LS, left total femur, or femoral neck BMD were discontinued from the trial. Secondary outcomes were the mean percentage change from baseline in LS BMD at weeks 26 and 52; left total femur BMD at weeks 26, 52, and end point as well as femoral neck BMD at weeks 26, 52, and end point. T-scores (the number of SDs above or below the mean BMD for a healthy 30-year-old subject of the same sex and ethnicity) were measured in the LS and left total femur.

Statistical methods

When assuming a dropout rate of at least 25% at the end of the 1-year study period, a total of 560 patients (140 per group) would yield approximately 100 patients per treatment group that completed the 1-year treatment period. A population of 100 patients per treatment group provided 80% power to detect a 1.2% difference between MF DPI 400 µg QD PM and ML after 1 year of treatment, with a pooled SD of 3%. BMDs at the LS and femur were assessed by using an ANOVA model by extracting sources of variation due to treatment and BMD scan center (Table I). All pairwise treatment comparisons were based on least squares mean values from the analysis model, and 2-sided 95% CIs were constructed for the estimated difference between the least squares mean values for treatment effects.

RESULTS

A total of 815 patients were screened for eligibility, with 566 randomized to treatment. Only 30 randomized subjects had

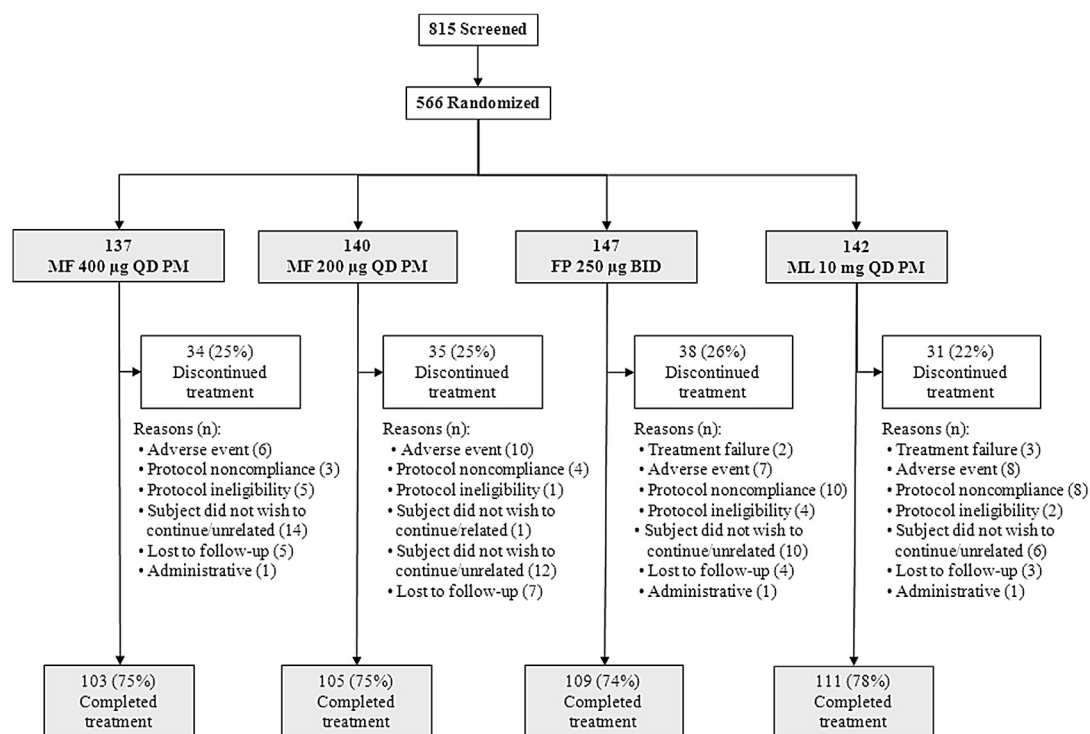


FIGURE 1. Disposition of patients.

TABLE III. Changes from baseline in BMD at 3 different loci at wk 26, wk 52, and the end point

BMD loci	% PSD	MF DPI 400 µg QD PM			MF DPI 200 µg QD PM			FP MDI 250 µg BID			ML 10 mg QD PM		
		No.	LSM	% LSM	No.	LSM	% LSM	No.	LSM	% LSM	No.	LSM	% LSM
LS, g/cm ²													
BL		121	1.09		117	1.10		131	1.11		127	1.10	
Change from BL													
Wk 26		109	0.005	0.5	106	0.008	0.8	118	0.010	0.9	111	0.010	1.0
Wk 52		99	0.013	1.3	98	0.007	0.6	102	0.014	1.3	104	0.015	1.4*
End point	2.56	121	0.009	0.9	117	0.008	0.7	131	0.012	1.1	127	0.013	1.2
Left total femur, g/cm ²													
BL		121	1.01		117	1.01		130	1.02		127	1.03	
Change from BL													
Wk 26		108	0.000	0.0	106	−0.001	0.0	118	0.002	0.3	110	0.003	0.4
Wk 52		100	0.003	0.3	97	0.005	0.6	101	0.005	0.5	104	0.006	0.6
End point	2.54	121	0.002	0.2	117	0.003	0.3	130	0.002	0.2	127	0.005	0.5
Femoral neck, g/cm ²													
BL		121	0.95		117	0.95		130	0.97		127	0.97	
Change from BL													
Wk 26		108	0.000	0.0	106	−0.002	−0.1	118	−0.006	−0.5	110	−0.002	−0.1
Wk 52		100	0.003	0.3	97	−0.003	−0.2	101	−0.003	−0.2	104	−0.001	0.0
End point	2.00	121	0.004	0.4†	117	−0.003	−0.2	130	−0.005	−0.4	127	−0.002	−0.2

BL, Baseline; FP MDI, fluticasone propionate delivered via metered dose inhaler; LS, lumbar spine; LSM, least squares mean; MF DPI, mometasone furoate delivered via dry powder inhaler; ML, montelukast sodium delivered by oral film-coated tablet; PSD, pooled standard deviation; QD PM, once daily in the evening.

**P* = .030 versus MF DPI 200 µg QD PM.

†*P* = .044 versus FP MDI 250 µg BID.

previously taken an ICS for asthma control (Table II); 29 of these subjects stopped previous ICS treatment at least 4 months before randomization, and 1 subject stopped 2 months before randomization, which was a deviation from the protocol. All randomized

patients received at least 1 dose of study treatment. A total of 428 patients completed the treatment phase (76%). One hundred thirty-eight patients (24%), distributed comparably across all medication groups, discontinued investigational treatment

TABLE IV. Estimated differences at end point in BMD at 3 different loci

BMD loci	MF 400 µg – ML, % (95% CI)	MF 200 µg – ML, % (95% CI)	FP – ML, % (95% CI)	MF 400 µg – FP, % (95% CI)	MF 200 µg – FP, % (95% CI)
LS	–0.3 (–1.01 to 0.27)	–0.5 (–1.14 to 0.15)	–0.1 (–0.77 to 0.48)	–0.2 (–0.85 to 0.42)	–0.4 (–0.99 to 0.29)
Left total femur	–0.3 (–0.73 to 0.27)	–0.2 (–0.67 to 0.34)	–0.3 (–0.71 to 0.28)	0.0 (–0.52 to 0.48)	0.1 (–0.45 to 0.55)
Femoral neck	0.6 (–0.24 to 1.35)	0.0 (–0.82 to 0.78)	–0.2 (–1.03 to 0.53)	0.8 (0.02 to 1.60)	0.2 (–0.56 to 1.03)

CI, Confidence interval; FP, fluticasone propionate; LS, lumbar spine; MF, mometasone furoate; ML, montelukast sodium delivered by oral film-coated tablet.

prematurely (Figure 1). Of 566 patients randomized to treatment, complete LS BMD data were available for 496 patients at the study end point (up to 52 weeks; $n = 121$, MF 400 µg; $n = 117$, MF 200 µg; $n = 130$, FP; $n = 127$, ML). The treatment groups were well balanced (Table II). Forced expiratory volume in 1 second was comparable across treatment groups at randomization, as was mean baseline LS BMD (range, 1.08–1.10 g/cm²).

For the primary outcome measurement, MF DPI administered for 1 year was not different from ML 10 mg. Treatment with MF 400 µg and 200 µg resulted in small increases (0.9% and 0.7%, respectively) in LS BMD at the end point. No significant differences were observed among any treatments at the end point ($P \geq .132$), including the primary comparison of MF 400 µg versus ML ($P = .261$). LS BMD did not decrease at any time point; on the contrary, LS BMD increased at least 0.5% in all treatment groups at weeks 26 and 52 (Table III). The only significant difference between treatments in change from baseline in LS BMD was a significantly greater increase with ML (1.4%) compared with MF 200 µg (0.6%; $P = .030$) at week 52. Overall, LS BMD did not decrease at any assessment and showed minor increases in each of the 4 treatment groups over the course of the study. The estimated BMD differences for MF 400 µg versus ML were –0.3% (95% CI, –1.01 to 0.27) for the LS, –0.3% (95% CI, –0.73 to 0.27) for the left total femur, and 0.6% (95% CI, –0.24 to 1.35) for the femoral neck (Table IV). There was no trend toward greater lumbar bone loss over time in any pairwise comparison of the study treatments. There was no apparent interaction between age, female sex, long-term ICS or ML treatment, and change in LS BMD.

The mean left total femur BMD was minimally increased in all treatment groups, with differences between treatments failing to achieve statistical significance. In the MF 400 µg, MF 200 µg, FP, and ML groups, mean changes from baseline in left total femur BMD were 0.2%, 0.3%, 0.2%, and 0.5%, respectively. Mean changes at end point in femoral neck BMD ranged from a 0.4% increase in the MF 400 µg group to a –0.4% decrease in the FP group, which was statistically significant ($P = .044$) (Table III). No other significant differences in femoral neck BMD changes were observed among treatment groups, although the MF 400 µg group was the only treatment group with an increase in femoral neck BMD. Older patients and female patients showed no deterioration in left total femur BMD with MF 400 µg, MF 200 µg, FP, or ML. Femoral neck bone mass was also maintained in women treated with MF 400 µg or MF 200 µg.

At the end point, T-score assessments showed that most patients in the 4 treatment groups were greater than –1.0 SD from the mean for LS BMD and left total femur BMD (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). For the LS BMD T-score, 1 patient (0.8%) in the MF 400 µg group was between 2.0 and 2.5 SD from the mean. For left total femur T-score, 1 patient (0.8%) in the MF

400 µg group and 1 patient (0.9%) in the MF 200 µg group was between 2.0 and 2.5 SD from the mean.

A small number of patients in all groups demonstrated a change in BMD of 6% or more at one or more bone sites after treatment initiation (5, MF 400 µg; 5, MF 200 µg; 10, FP; 7, ML). By protocol, these patients were discontinued from the study. All the treatment groups had more patients with BMD loss $\geq 6\%$ in the femoral neck than in the LS or left total femur. Exposure to treatment was apparent as changes quantified by spirometry (see Table E2 in this article's Online Repository at www.jaci-inpractice.org) and patient-reported improvements in symptoms, and rescue medication use decreased in all treatment groups (data not shown). Systemic exposure to MF was reflected in mean changes from baseline in cortisol 24-hour area under the curve values obtained at selected centers. When 4 outliers with extreme increases or decreases in serum cortisol were excluded from the evaluation, mean serum cortisol decreased 11.8% in the MF 400 µg group ($n = 14$) and 7.8% in the MF 200 µg group ($n = 14$); it decreased 2.7% in the FP group ($n = 18$) and increased 10.5% in the ML group ($n = 15$).

All 4 study treatments were generally safe and well tolerated, with no unusual or unexpected AEs. One patient each in the MF 200 µg, MF 400 µg, and FP groups discontinued due to ocular hypertension, and 1 patient in the MF 400 µg group discontinued due to lenticular opacities. Three patients reported serious AEs possibly or probably related to treatment, one in the ML group with pleural effusion and pneumonia, one in the ML group with keratitis herpetic, and one in the MF 400 µg group with lenticular opacities. Overall, two-thirds of the patients reported AEs, with most being unrelated to study treatment. The most commonly reported AEs were nasopharyngitis (16% overall), headache (14% overall), and pharyngitis (10% overall). Treatment-emergent oral candidiasis occurred in 2 patients overall: one in the MF 400 µg group and one in the FP group. The overall percentage of patients who reported AEs that were considered treatment related by investigators was low (12%), and the most commonly reported treatment-related AE was headache, reported by 10 patients (2% overall).

DISCUSSION

This study demonstrated that bone density was maintained among adult patients who took calcium and vitamin D supplements, and treated for 52 weeks with an ICS such as QD MF DPI or BID FP, or with QD ML. It is important to note that this study randomized 566 patients to 1 year of treatment, which is at least 50% more patients than other randomized prospective studies of BMD in ICS users.^{15–20} We observed that administration of MF for 1 year had effects on LS BMD that were not different from those seen among patients treated with ML, a leukotriene antagonist with no known effects on BMD.

Contrary to investigations in the published literature that showed reduction in BMD after chronic exposure to a range of ICS formulations and delivery devices; however, patients in the present study experienced minor gain, rather than loss, in lumbar BMD.

For LS BMD results, we did not identify any statistically significant differences between MF 400 µg and ML, the primary comparison. Although the difference between increases from baseline in LS BMD with MF 200 µg and ML was statistically significant, it probably was not clinically meaningful. Subgroup analyses by age or sex also confirmed the absence of any adverse effect on LS bone mass. Similarly, no decrease from baseline was observed for left total femur BMD in any of the treatment groups, and no statistically significant differences were found among treatment groups. It is important to note that one may observe 5% variability in BMD in repeated testing and that the inclusion criteria of 5% agreement on initial examination may weaken the evidence for safety in this study.

A previous study of MF DPI 200 µg administered BID showed a small but measurable effect of reduced LS BMD after 2 years of treatment in patients not previously maintained on ICS therapy.¹⁴ The effect on BMD seen with MF was a recognized effect of the drug class, and the results were not inconsistent with results seen for other ICSs. BMD effects occurred mainly in the first year of previous MF DPI studies, and the 1-year duration of the current study was considered sufficient to evaluate the possible effects of MF DPI on BMD. However, the relatively short (1 year) treatment period of the current study does not address the issue of safety associated with more long-term use. Another difference from the previous MF DPI studies was the requirement in the current study for sufficient vitamin D and calcium levels as a study inclusion criterion with the use of vitamin D and calcium supplements. As such, our study findings may not be generalizable to patients not taking calcium and vitamin D.

In the present study, a minor difference between MF 400 µg and FP in femoral neck BMD at the end point was the only statistically significant difference between treatments for this variable. It is important to note that the femoral neck is considered to be a region of high variability for BMD measurement. Several cross-sectional studies have demonstrated a measurable effect of ICS as a class, especially when administered in high doses to women.^{4,6-9} In contrast, other longitudinal studies of inhaled beclomethasone dipropionate, budesonide, or FP have shown little or no significant effect on BMD.¹⁵⁻²¹ The variation in results of published studies may be attributable to differences in study design, populations, and individual characteristics of the ICS, including oral bioavailability and glucocorticoid receptor binding affinity. It is important to note that other published ICS studies either did not use BMD-loss discontinuation criteria^{4,6,9,17-21} or used discontinuation for BMD decline only at the LS,^{15,16} the locus for primary analysis. Some published studies conducted in patients with moderate-to-severe asthma treated chronically with high daily doses of ICS and bursts of oral corticosteroids have failed to demonstrate a significant effect of ICS on BMD.¹⁸⁻²⁰ Individuals who are corticosteroid-naïve (or who have not been treated with ICS for extended periods of time) may be more susceptible to low levels of BMD loss than those who have had prior repeated exposure to corticosteroids.

An effect on BMD with prolonged ICS exposure has been consistently demonstrated in older perimenopausal women.⁴ All female participants in this study were young adults, through

40 years of age, to minimize confounding due to bone loss associated with menopause. We observed no adverse safety interaction between any dose of MF and female or male sex in this study. Female patients in all treatment groups had small increases in LS BMD, whereas male patients in the MF 400 µg group had a small decrease in LS BMD.

In addition to bone changes associated with menopause in woman and older age in both men and women, BMD is adversely affected by vitamin D and calcium deficiency, and by diseases that promote a sedentary lifestyle or otherwise restrict normal activity.²² Participants in this study received a daily vitamin D and calcium supplement, and compliance with treatment was satisfactory. Although we did not compile physical activity scores in this study, we enrolled a relatively young cohort and excluded a comprehensive range of conditions known to be associated with a high risk of osteoporosis or to predispose to limited activity. Because poorly controlled or severe asthma may restrict physical activity,²³ and, because higher degrees of respiratory impairment may be inherently pathogenic to BMD in older patients by other mechanisms,²⁴ we studied only younger patients with mild-moderate persistent asthma who demonstrated a satisfactory response at baseline to bronchodilator treatment.

All treatment groups in the present study demonstrated improvement in lung function and asthma symptoms while reducing the use of rescue medication, which reflected patients' exposure to study treatment. In addition, observed changes in serum cortisol were not considered clinically meaningful, although they demonstrated exposure to study treatment. All study treatments were safe and well tolerated. There were no unusual AEs and no treatment-related mortality. The majority of AEs were mild or moderate in severity, and the number of treatment-emergent AEs was similar among the different treatment groups. There were few serious AEs; when present, most were considered by the investigators as unlikely related to treatment. Laboratory values by treatment group demonstrated no clinically relevant changes in median values over the course of the study.

CONCLUSION

This study confirmed that use of MF DPI for 1 year was well tolerated and safe in relatively young patients with asthma and no other predisposition to bone loss. There were no observed detrimental effects on BMD at either dose that was evaluated in patients who received calcium and vitamin D supplements. These findings provide important evidence and necessary guidance regarding the effects on BMD during prolonged treatment with inhaled MF administered QD in the evening at either 400 µg or 200 µg. Further studies will be needed to evaluate the potential impact of ICS for older patients with asthma or for those with other risk factors for bone loss.

Acknowledgments

Assistance in statistical analysis was provided by Davis Gates, PhD, Merck & Co Inc, Whitehouse Station, NJ. Medical writing and editorial assistance was provided by Buz Abrams, MD, and Ken Kauffman, BSc, Adelphi Communications New York, New York, NY. This assistance was funded by Merck & Co Inc, Whitehouse Station, NJ. Editorial assistance was also provided by Jorge Moreno-Cantu, PhD, Global Scientific and Medical Publications, Office of the Chief Medical Officer, Merck & Co Inc, Whitehouse Station, NJ.

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TABLE E1. Summary of T-scores at end point for LS BMD and total femur BMD (all randomized patients)

T-scores (SD)*	MF DPI 400 µg QD PM (n = 121)	MF DPI 200 µg QD PM (n = 117)	FP-MDI 250 µg BID (n = 131)†	ML 10 mg QD PM (n = 127)
LS, no. (%)				
<2.5 to <-2	1 (0.8)	—	—	—
-2 to -1	23 (19.0)	25 (21.4)	17 (13.0)	23 (18.1)
>-1	97 (80.2)	92 (78.6)	114 (87.0)	104 (81.9)
Left total femur, no. (%)				
<2.5 to <-2	1 (0.8)	1 (0.9)	—	—
-2 to -1	10 (8.3)	8 (6.8)	12 (9.2)	9 (7.1)
>-1	110 (90.9)	108 (92.3)	118 (90.8)	118 (92.9)

*SD indicates number of standard deviations above or below the mean BMD for a healthy 30-year-old of the same sex and ethnicity.

†n = 130 for the left total femur.

TABLE E2. Summary of baseline values and changes at the end point in pulmonary function tests (all randomized patients)*

	MF DPI 400 µg QD PM (n = 136)		MF DPI 200 µg QD PM (n = 140)		FP-MDI 250 µg BID (n = 146)		ML 10 mg QD PM (n = 141)	
	LSM	Percentage	LSM	Percentage	LSM	Percentage	LSM	Percentage
FEV ₁ (L)								
Baseline	2.66		2.60		2.64		2.70	
Change at end point	0.38	14.7	0.29	11.7	0.31	12.6	0.19	7.2
FEF _{25%-75%} (L)								
Baseline	2.21		2.28		2.22			
Change at end point	0.55	30.9	0.42	27.0	0.48	31.1	0.25	14.6
FVC (L)								
Baseline	3.60		3.49		3.60		3.61	
Change at end point	0.26	7.4	0.17	5.9	0.22	6.8	0.14	4.2
FEV ₁ % predicted								
Baseline	76.41		74.72		75.28		76.87	
Change at end point	10.69	14.7	8.41	11.7	9.04	12.6	5.15	7.2

FEF_{25%-75%}, Forced expiratory flow at 25% to 75% of vital capacity; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LSM, least squares mean.

*All study medications were associated with general improvements in asthma control over the course of the study, evaluable by changes in lung function parameters and general symptom improvement. Mean changes from baseline were consistently greater in the ICS groups compared with the ML group. A clinical asthma deterioration is an episode that results in emergency treatment, hospitalization, or treatment with additional asthma medication (other than short-acting inhaled β-agonists).