Mometasone furoate in the management of asthma: a review

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Abstract: Inhaled corticosteroids (ICS) have proven to be the most effective and essential therapy for the treatment of bronchial asthma. The 2007 National Asthma Education and Prevention Program guidelines recommend ICS as preferred therapy for patients with mild to severe persistent asthma. Mometasone furoate (MF) is a relatively new ICS agent with high affinity for the glucocorticoid receptor. It is approved in the US for maintenance treatment of asthma for patients 4 years of age and older. It has been shown to be well tolerated with no significant adverse side effects observed in clinical trials and post-marketing surveillance. The efficacy of mometasone furoate has been established in large, well-designed studies. In patients with persistent asthma previously treated either with short-acting beta-agonists alone or twice-daily maintenance therapy with ICS, once-daily MF has been shown to be superior to placebo in improving lung function, symptom control, and quality of life; and has shown comparable efficacy compared with budesonide, beclomethasone, and fluticasone. Twice-daily dosing with MF has been demonstrated to successfully allow for reduction or elimination of oral corticosteroids in severe asthmatics.

Keywords: inhaled steroids, mometasone furoate, once-daily dosing, asthma, stepwise approach

Introduction

Over the past two decades, inhaled corticosteroids (ICS) have been demonstrated to be the most effective treatment for persistent asthma. ICS act on the glucocorticoid receptor to inhibit the release of cytokines and inflammatory mediators, decrease eosinophil and mast cell recruitment, suppress adhesion molecule function and inducible nitric oxide synthase (National Heart, Lung and Blood Institute 2007). These cellular effects translate clinically into significant improvements in pulmonary function and asthma symptoms as well as reductions in exacerbations requiring oral corticosteroids, emergency room care, and hospitalization (National Heart, Lung and Blood Institute 2007). Further, this class of drugs has been demonstrated to be the most effective class of asthma medications compared with other drugs (National Heart, Lung and Blood Institute 2007). The most recent National Asthma Education and Prevention Program guidelines recommend ICS as preferred therapy for all severity levels of asthma (National Heart, Lung and Blood Institute 2007).

Mometasone furoate (MF) is the first ICS approved for once-daily dosing in the US and was approved for patients 12 years and older in 2005 and for children 4 to 11 years of age in 2008. It is marketed as Asmanex™ with 110 μg and 220 μg per actuation in a multidose dry powder breath-actuated device (Twisthaler™). The 220 μg form delivers 200 μg of mometasone furoate per actuation while the 110 μg form delivers 100 μg mometasone furoate per actuation. The recommended dosages are 220 μg to 440 μg once daily in the evening (or in 2 divided doses) for patients 12 years and older previously treated with either bronchodilators alone or with ICS. The recommended dose for

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patients requiring daily treatment with oral corticosteroids is 440 μg twice daily. The only recommended dose for children 4 to 11 years is 110 μg once daily in the evening.

Chemistry

MF is a synthetic, 17-heterocyclic conrticosteroid with a very high affinity for the glucocorticoid receptor. The chemical name of MF is 9α, 21-dichloro-11β,17α-dihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione17-(2')-furoate. Its molecular formula is $C_{27}H_{30}O_6Cl_2$. In vitro studies show that MF binds to a monomeric glucocorticoid receptor at low concentrations and at high concentrations causes dimerization of the glucocorticoid receptor. The receptor affinity of MF has been estimated to be 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone (Crim et al 2001).

Pharmacology

MF is extensively metabolized in the liver by the CYP3A4 enzyme system with only a minor metabolite, 6β-hydroxy-MF (Affrime and Kosoglu 2001). This metabolite is not detectable in plasma after single and multiple doses of MF- (dry powder inhaler) DPI, making it unlikely that it would affect the hydroxylation of other drugs metabolized by CYP3A4 (Karpel and Nelson 2007). In vitro studies have demonstrated that there may be as many as 5 metabolites and 4 degradation products of MF (Ten et al 2003; Sahasranaaman et al 2006). Study doses were mainly excreted in the feces with a small amount in the urine (74 % and 8% respectively) (Karpel and Nelson 2007). Pharmacologic studies of MF in which a single 1000 μg dose of tritiated (3H-) MF was administered by DPI to healthy subjects showed that the plasma concentration were below the limit of quantification (LOQ = 50 pg/mL) in 92% of subjects. These initial data suggested that the bioavailability of inhaled MF is less than 1% (Affrime et al 2000). However, other investigations have indicated that the true bioavailability of MF is higher and similar in magnitude to that of other ICS (Derendorf et al 2002).

In vitro studies have demonstrated that MF has a very high binding affinity for human glucocorticoid receptor. Valotis et al (2004) showed that the relative receptor affinity for MF is 2200 compared with 100 for dexamethasone and 1800 for fluticasone propionate. In that same study, dissociation of the MF-receptor complex was faster than that observed for fluticasone, allowing for faster redistribution of the drug from lung tissue into the plasma. The relative receptor affinity of 6-beta-hydorxy MF has been shown to be significantly lower than the parent compound and is similar in activity to that of flunisolide (206 and 180 for MF and flunisolide, respectively) (Valotis and Högger 2004).

Clinical efficacy (Table 1)

Once-daily dosing in patients only on SABAs

Two randomized, double blind studies have confirmed the efficacy of once-daily dosing of MF-DPI compared with placebo in steroid-naïve patients only on SABAs.

In a study by Bensch et al (2006), 196 adult and adolescent asthmatics were randomized to either MF 200 μg once daily in the evening or placebo for 12 weeks. The study demonstrated that MF was well tolerated and showed a significant improvement from baseline FEV_1 of 0.43 L (16.8%) compared with placebo of 0.16 L (6%) ($p < 0.01$). There was also significant improvement in forced vital capacity (FVC), forced expiratory flow (FEF) 25% to 75%, and peak expiratory flow (PEF) in the treatment group compared with placebo. There were no significant differences between the two groups in the time to worsening of asthma. Other efficacy variables of asthma symptom scores, rescue albuterol use, and nocturnal awakenings were also not significantly different in the two groups. The authors felt that the results showed that a relatively low dose of MF 200 μg was significantly better than placebo in the steroid-naïve population.

In a second study of 236 steroid-naïve adolescent and adult asthmatics by Nayak et al (2000), 2 doses given once daily in the morning (200 μg and 400 μg) were compared with placebo assessments. The study results showed that both doses of MF were well-tolerated. For FEV_1, both the 200 μg and 400 μg once-daily doses showed superior efficacy at 14.8% and 14.2% respectively, compared with placebo (2.5%) but no significant difference between each other. Most of the secondary efficacy variables were significantly improved with both doses compared with placebo. An important finding was that the morning PEF was significantly superior to placebo with the 400 μg dose but not with the 200 μg dose. The authors suggested that 400 μg should be the starting dose with reduction later likely to the 200 μg dose (Nayak et al 2000).

Once-daily versus twice-daily dosing in patients on SABAs only

In a 12-week study by Kemp et al (2000) with 306 mild to moderate asthmatic subjects using inhaled SABAs only, MF given once daily (200 μg q AM or 400 μg q AM) or twice

daily (200 μg bid) were compared with placebo. There was significant improvement with both the 200 μg bid (16.1%) and 400 μg q AM (16.0%) dosing over placebo (5.5%) in mean change from baseline in FEV_1. However, the 200 μg q AM (10.4%) dosing did not show a significant difference from placebo. The secondary efficacy variables similarly improved significantly over placebo with a total daily dosing of 400 μg, whether given as a qd or bid dosing. All the doses were well tolerated.

Once daily versus twice daily dosing in patients previously maintained on ICS

Noonan et al (2001) randomized 286 mild to moderate asthmatics using twice-daily ICS to receive either MF once daily (200 μg q AM, 200 μg q PM or 400 μg q AM) or twice daily (200 μg bid) or placebo for 12 weeks. This was preceded by a 2-week open-label phase where all subjects received MF 200 μg bid. To obtain data on possible HPA axis suppression, cosyntropin stimulation tests were done on 20 to 24 subjects in each treatment group. Results showed that all doses were well tolerated. There was an expected increase in the mean baseline FEV_1 (2.52 to 2.65 L) after the open-label run-in period on MF 200 μg bid. This increase was maintained with the 400 μg qd (–0.01), 200 μg bid (–0.03), and 200 μg q PM (0.03) doses compared with placebo (–0.30). However, the 200 μg q AM dose (–0.22) did not do better than placebo, suggesting that evening dosing might be more effective. The 400 μg qd dose provided the most consistent improvement in the secondary efficacy variables. The cosyntropin stimulation test results demonstrated that a similar proportion of subjects had normal responses in the treatment and placebo groups. This study was one of the first to show that once-daily dosing could maintain effective control in patients previously on twice-daily dosing.

In a 12-week study with 400 subjects by D'Urzo et al (2005), the primary objective was to compare the efficacy and safety of once-daily MF-DPI 400 μg q PM with placebo. A secondary objective was to compare several MF dosing regimens with each other and placebo. Subjects were all previously on stable bid ICS for at least 30 days and were randomized to one of 4 dosing regimens of MF: 200 μg q PM; 2 inhalations of 200 μg q PM; 200 μg bid; or placebo. All the MF doses showed significant improvement over placebo with mean changes from baseline FEV_1 of 0.41L (400 μg q PM), 0.49 L (200 μg 2 inhalations q PM), 0.41L (200 μg q PM), 0.51 L (200 μg bid), and 0.16 L (placebo) ($p < 0.001$). All of the treatment doses were well tolerated and improved secondary efficacy variables. This study confirmed the efficacy of the 400 μg evening dose, whether given as one 400 μg inhalation or two 200 μg inhalations. The lowest dose of 200 μg q PM also appeared to be similarly effective.

Similar results were obtained in a study of 268 subjects by Karpel et al (2005). Patients were 12 years of age or older and previously on stable ICS bid for at least 30 days with FEV_1 between 50% to 85% of predicted. The treatments in the study included MF 400 μg q PM, MF 200 μg bid and placebo. Both MF doses were well tolerated with mean change from baseline FEV_1 significantly improved over placebo. The once daily MF 400 μg was as effective as twice daily MF 200 μg bid in improving the primary secondary efficacy measures.

MF in children

Berger et al (2006) published the results of a study of MF-DPI in 296 asthmatic children. Children were enrolled of 4 to 11 years of age with mild to moderate asthma, an FEV_1 of 60% to 85% of predicted, and on stable ICS doses for at least 60 days. The subjects were randomized to receive either 100 μg once daily in the evening, 100 μg bid, or placebo. The authors indicated that the inclusion of a placebo was justified because patients who worsened were to be discontinued and use of short-acting beta-agonists was allowed. Both treatment groups showed significant improvement of FEV_1 from baseline compared with placebo ($p \leq 0.002$). The least squares mean changes in the percentage of predicted FEV_1 were 4.73 (MF qd) and 5.52 (MF bid) compared with –1.77 (placebo). There was no significant difference in effectiveness between the two doses ($p = 0.70$). FVC, FEF 25% to 75%, and PEF were superior for both doses compared with placebo but with no significant difference between the doses. The other secondary variables, including asthma symptom scores, rescue medication use, and HR QoL assessments all showed that the MF groups were similar to each other but superior to placebo. Fewer than 50% in the MF treatment groups had worsening of asthma so the median time to worsening could not be determined. Overall, this study showed the efficacy and safety of the MF-DPI 100 μg once daily evening dosing in children.

Reduction of oral steroids in severe asthma

The use of chronic oral corticosteroids (OCS) is necessary in a small population of patients with severe asthma. Reduction or elimination of OCS use is an important goal in these

Table 1 Clinical studies

Investigators	Design	Study doses	Results
qd, SABA only			
Bensch et al 2006	N = 196, 12 week, PC Primary outcome: change in FEV_1	200 μg q AM	Improvement with 200 μg (16.8%) vs placebo (6%)
Nayak et al 2000	N = 236, 12 week, PC Primary outcome: change in FEV_1	200 μg q AM 400 μg q AM	Both doses better than placebo but 400 μg provided additional improvement
qd vs bid, SABA only			
Kemp et al 2000	N = 306, 12 week, PC, Primary outcome: change in FEV_1	200 μg q AM, 400 μg q AM 200 μg bid	Total of 400 μg/day effective, either in qd or bid regimen Change in FEV_1 for 200 μg bid (16.1%), 400 μg qd (16.0%) significant over placebo (5.5%)
qd vs bid, previous ICS			
Noonan et al 2001	N = 286, 12 week, PC, Primary outcome: change in FEV_1	200 μg bid, 200 μg q AM, 200 μg q PM, 400 μg q AM	400 μg q am maintained FEV_1, lung function, symptom scores 200 μg q PM improved FEV_1, not other measures 200 μg q AM not as effective
D'Urzo et al 2005	N = 400, 12 week, PC, Primary outcome: change in FEV_1	200 μg QD, 400 μg 1 inhal qd PM 400 μg (2 inhal of 200 μg) qd PM 200 μg bid	All doses better than placebo, including lowest dose. Similar improvement for all doses
Karpel et al 2005	N = 268, 12 week, PC, Primary outcome: change in FEV_1	400 μg q PM, 200 μg bid	Both doses better than placebo. Similar improvement for all doses
Pediatric			
Berger et al 2006	N = 296, 12 week, 4–11 y.o.	100 μg q AM, 100 μg bid	Both doses better than placebo. Similar improvement for all doses
Reduced oral steroids in severe asthma			
Fish et al 2000	N = 262, 12 week PC then 9 month open-label	400 μg bid 800 μg bid	OCS reduced by 46% (400 μg) , 23.9% (800 μg), increased by 164.4% (placebo) OCS eliminated in 40% (400 μg), 37% (800 μg) , 0% (placebo) Lung function and QofL improved
Karpel et al 2007	N = 123, 12-week, PC then 9-month open label	HFA-227 MDI 400 μg bid 800 μg bid	OCS reduced by 39.4% (400 μg), 31.1% (800 μg), increased by 107.2% (placebo) OCS reduced by ≥50% in 63% (400), 60% (800), 14% (P) Overall results: (with open label extension) 67% OCS reduction, 51% OCS elimination
Schmier et al 2003	Open label extension of Fish et al (2000)	400 μg bid 800 μg bid	SF-36 HRQL (QofL) maintained or improved for 3 months of open label extension
Comparative			
Bousquet et al 2000	N = 12 week, AC Primary outcome: change in FEV_1	MF 100, 200, 400 μg bid, BUD 400 μg bid	MF 200, 400 bid superior to BUD 400 bid; MF 200 = 400 bid Conclusion: total 400 μg MF/day better than 800 μg BUD/day

(*Continued*)

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Investigators	Design	Study doses	Results
Chervinsky et al 2002	N = 395, 4 week , PC Dose ranging, Primary outcome: change in FEV_1	MF-MDI 56, 200, 500 pg bid, BDP 168 μg bid	MF 200 pg bid better than MF 56 pg bid and BDP 168 μg bid All doses improved lung function, symptom scores, QOL No additional benefit from MF 500 pg bid
Corren et al 2003	N = 262, 8 week, PC Primary outcome: change in FEV_1	MF 440 μg q AM BUD DPI q AM	MF-DPI (8.9%) superior to BUD DPI (2.1%) or placebo (–3.9%)
Nathan et al 2001	N = 227, 12 week, PC Primary outcome: change in FEV_1	MF 100 μg or 200 μg bid BDP 168 μg bid	All doses better than placebo MF 200 μg bid most effective
O'Connor et al 2001	N = 733, 12 week, AC Dose-ranging Primary outcome: change in FEV_1	MF 100,200, or 400 μg bid FP diskhaler 250 μg bid	All doses improved outcome MF 400 μg /day comparable to FP 500 μg per day MF 800 μg /day no additional benefit. MF 200 μg /day least effective
Wardlaw et al 2004	N = 167, 8-week, open label, on previous FP Primary outcome: change in FEV_1	MF 400 μg q PM FP MDI 250 μg bid	"Comparable efficacy" between MF (4.58%) and FP (6.98%)

Abbreviations: AC, active controlled; BUD, budesonide; FEV_1, forced expiratory volume in 1 second; PC, placebo controlled; FP, fluticasone proprionate; MDI, metered dose inhaler; MF, mometasone furoate; OCS; chronic oral corticosteroids.

patients and is often employed as the "gold standard" for new therapies directed at this severe subgroup of asthmatics.

Fish et al (2000) studied the effect of MF in a 12-week study that randomized 132 subjects with severe, OCS-requiring asthma. The subjects were 12 years of age or older who had required daily or alternate-day OCS for asthma control for 5 or more of the 6 months before enrollment with FEV_1 40% to 85% of predicted. The minimum effective prednisone dose was determined for each subject either by previous documentation in the previous 6 months or before screening by the investigator who reduced the dose in a stepwise manner until pulmonary function declined. Subjects receiving a minimum effective prednisone dose of 5 to 30 mg daily or 10 to 60 mg every other day were eligible for the study. After a 2-week run-in period with the subjects continuing their usual ICS and minimum effective prednisone dose, they were randomized to either MF-DPI 400 μg bid, MF 800 μg bid, or placebo and their pre-study ICS was stopped. The primary outcome measure was the percentage change from baseline in daily prednisone requirement. A significantly larger proportion of subjects on placebo (55%) compared with those on MF 400 μg bid (7%) and MF 800 μg bid (12%) discontinued due to treatment failure and worsened asthma. The primary outcome measure showed that the MF 400 μg bid (–46%) and MF 800 μg bid (–23.9 %) decreased prednisone use very significantly compared with placebo (+164.4%) ($p < 0.01$). Sixty-two percent of those on MF 400 μg bid and 62% of those on 800 μg bid reduced prednisone dose by 50% compared with 7 % of the placebo group. Complete elimination of prednisone use was seen in 40% of the MF 400 μg bid group and 37% of the MF 800 μg bid group, compared with 0% in the placebo group. Indices of pulmonary function, symptom scores, and QoL measures were also improved significantly in the MF treatment groups compared with placebo. The increase in prednisone use in the placebo group was expected because the subjects' usual ICS were stopped prior to randomization. The authors noted that this observation supported the presence of true OCS-dependent asthma in this group. Both MF doses were well-tolerated with comparable results between the two MF doses leading the authors to conclude that the MF 400 μg bid dose is a safe and effective alternative to OCS in severe asthma. The steroid-sparing benefits of MF were maintained in a 9-month open label extension phase (Schmier et al 2003).

Using similar methods and outcome measures, a more recent trial studied MF (delivered in the hydrofluoroalkane [HFA]-227 metered dose inhaler [MDI] device) in 123 OCS-dependent severe persistent asthmatics (Karpel et al 2007). Subjects were randomized to receive either MF-MDI 400 μg bid, MF-MDI 800 μg bid, or placebo for 12 weeks followed by a 9-month open label phase. Daily prednisone doses were reduced in those on MF-MDI 400 μg

bid by 39.4 % and 800 μg bid by 31.1% while it increased by 107.2% in the placebo group ($p < 0.01$). Oral steroid use was reduced by at least 50% in the MF-MDI 400 μg bid, MF-MDI 800 μg bid, and the placebo groups by 63%, 60%, and 14% respectively. Overall, in the 12-week trial and the 9-month extension, there was a 67% reduction in prednisone requirements and 51% of subjects eliminated oral steroid use in those receiving MF-HFA.

Comparison with budesonide (BUD)

In a large active-controlled study by Bousquet et al (2000), 730 subjects in 17 countries with moderate persistent asthma on stable ICS for at least 30 days with FEV_1 of 60% to 90% of predicted, were randomized to one of three doses of MF (100 μg bid , 200 μg bid, 400 μg bid) or BUD turbohaler 400 μg bid. The results showed significantly superior improvement in the primary efficacy variable with MF 200 μg bid (0.16 L) and 400 μg bid (0.16 L) compared with BUD 400 μg bid (0.06 L), which was comparable with the lowest MF dose of 100 μg bid (0.10 L). Secondary parameters reflected the same results. All the treatment doses were well-tolerated. In this study, a total daily dose of MF 400 μg appeared to be more effective than a total daily dose of BUD 800 μg (Bousquet et al 2000).

Once-daily MF was also compared with once-daily BUD in a placebo-controlled 8-week study by Corren et al (2003). Two hundred and sixty-two subjects with moderate persistent asthma previously on stable bid ICS were randomized to either MF-DPI 440 μg q AM, BUD-DPI 400 μg q AM, or placebo. The primary efficacy variable was mean change from baseline FEV_1. In this study, MF 440 μg q AM showed significantly better improvement in mean percentage change in FEV_1 (8.9%) compared with BUD 400 μg q AM (2.1%) and placebo (–3.9%).

Comparison with beclomethasone diproprionate (BDP)

In a 4-week dose-ranging study with 395 subjects, several doses of MF given bid by MDI (56 μg, 200 μg, 500 μg) were compared with BDP 168 μg bid or placebo (Chervinsky et al 2002). Both drugs in this study were delivered in MDI devices containing chlorofluorocarbon vehicle. Subjects with moderate asthma, with FEV_1 50% to 90%, and stable ICS were randomized. All of the ICS treatment groups showed significant improvement of 6% (56 μg MF), 13% (200 μg MF), 14% (500 μg MF), and 4% (BDP) compared with placebo (–12%). The results suggested that the MF 200 μg bid and MF 500 μg bid doses are equivalent with both being superior in efficacy over the BDP 169 μg bid dose. All doses were well tolerated.

A longer, 12-week, placebo-controlled study by Nathan et al (2001) enrolled 227 subjects with moderate persistent asthma with FEV_1 60% to 90% already maintained on ICS for at least 30 days. Subjects were randomized to receive either MF-DPI 100 μg bid, MF-DPI 200 μg bid, BDP-MDI 168 μg bid, or placebo. All of the doses were tolerated well. With regard to efficacy, all of the active groups showed significant improvement in FEV_1 over placebo (–0.21 L) ($p < 0.01$, all comparisons). However, the MF 200 μg bid dose showed a 2-fold improvement (0.25 L) over MF 100 μg bid (0.12 L) and BDP 168 μg bid (0.11 L). This study shows that MF 200 μg bid is more efficacious in improving lung function and symptom scores compared with MF 100 μg bid and BDP-MDI 168 μg bid. The authors noted that the DPI produces high dose uniformity because it does not require hand/breath coordination and that this may contribute to better results with the DPI compared with the MDI.

Comparison with fluticasone proprionate (FP)

A large active-controlled study conducted in 20 countries by O'Connor et al (2001), with 732 subjects, compared the efficacy and safety of MF-DPI with the FP Diskhaler® 250 μg bid as the active control. Subjects were already on stable ICS doses for at least 30 days and had baseline FEV_1 at 60% to 90% of predicted. Subjects received either one of three doses of MF-DPI (100 μg, 200 μg, or 400 μg bid) or FP Diskhaler 250 μg bid. All MF doses and FP improved FEV_1 from baseline with a total daily dose of MF 200 μg bid dose (0.16 L) comparable with FP 500 μg per day (0.16 L). MF 100 μg bid was the least effective (0.07 L) while MF 400 μg bid (0.19 L) offered no additional benefit. Greater improvement was also seen in the secondary variables for the MF 200 μg and 400 μg bid and FP groups compared with the MF 100 μg bid group (O'Connor et al 2001).

Wardlaw et al (2004) conducted an open-label 8 week study of 167 subjects with moderate persistent asthma on previously stable FP for at least 30 days. Subjects were required to have an FEV_1 of 60% to 90% of predicted and were randomized to receive either MF-DPI 400 μg q PM or FP MDI 250 μg (two 125 μg inhalations) bid. Mean changes from baseline FEV_1 for the MF-DPI and FP groups were 0.11 L (4.58%) and 0.16 L (6.98%), respectively ($p = 0.35$). Both drugs were well tolerated, with significantly more subjects who "liked the inhaler a lot" in MF-DPI group

(46.8%) than in the FP group (22.4%) (p = 0.01). This open label study confirmed comparable efficacy between a total daily dose on MF 400 μg q PM and FP 500 μg qd.

The most recent comparison between these two inhaled compounds was published by Harnest et al (2008). In this 12-week non-inferiority trial of patients with moderate-to-severe persistent asthma, there were no significant between-group differences in lung function, rescue medication use, response to therapy, exacerbation rates, or adverse events between MF-DPI 400 μg twice daily or FP-DPI 500 μg twice daily. Based on these results, these medications appear to be roughly equivalent in effectiveness on a microgram basis.

Safety and tolerability

In general, the potential for side effects from ICS is small and the benefits far outweigh any risks (National Heart, Lung and Blood Institute 2007). However, local and occasionally systemic side effects may occur with ICS, especially at high doses. Oral candidiasis can be seen and mouth-rinsing after each inhalation should always be strongly advised for patients. Systemic effects such as adrenal suppression, cataracts, glaucoma, and decreased bone mineral density in adults, and adrenal suppression and decreased growth velocity in children are possible with high doses of inhaled steroids but are much less likely than with oral or parenteral steroids.

In clinical studies in both children and adults, MF has been shown to be well tolerated; oral candidiasis was the most frequently observed treatment-related adverse event (Meltzer et al 2006). Studies of HPA axis suppression have revealed only minimal effects by MF. In one study comparing the HPA axis effects of MF and FP, the free plasma concentration producing 50% urinary cortisol suppression (IC_{50}) was similar for both compounds indicating the same potential to cause systemic side effects (Tayab et al 2007). Adrenal suppression as measured by overnight urinary cortisol/creatinine in a study with 21 patients also suggested similar significant suppression by both MF and FP dry powder formulations (Fardon et al 2004). In a study of MF delivered by DPI or MDI, doses of up to1600 μg daily for 28 days showed minimal HPA axis suppression as measured by serum cortisol concentration area under the curve over 24 hours (AUC 24) and consyntropin response test (Affrime et al 2000). In a study comparing MF-DPI 400 μg qd with beclomethasone diproprionate (BDP) HFA 200 μg 2 puffs bid and BDP-CFC 400 μg 2 puffs bid for 14 days, the serum cortisol AUC24 decreased to a lesser degree with MF than with the two formulations of BDP (Chrousos et al 2005).

Studies of MF effects on bone mineral density (BMD) have been conducted for periods up to 2 years in duration. At the 2-year endpoint, there was no statistically significant in lumbar spine BMD in patients using 400 μg bid compared with a placebo group (Mortimer et al 2005).

Decreases in growth velocity may be observed in children taking with ICS but long-term follow-up studies have shown that the expected adult heights are usually achieved (Agertoft and Pedersen 2000; Gulliver et al 2007). The effect of MF on growth in children has been followed for up to 1 year in clinical studies (Skoner et al 2003; Lemanske et al 2004). In a 1-year study, there was no difference in growth velocity between patients taking MF-DPI 100 μg qd (6.42 cm/year) and placebo (6.52 cm/year), but a slight but statistically significant difference was observed with patients taking 200 μg qd (5.82 cm/year).

Conclusion

MF is a potent ICS with strong affinity for the glucocorticoid receptor. It is currently approved for use in 40 countries including the UK and EU down to the age of 4 years. It is well tolerated with no significant adverse side effects seen in post-marketing surveillance different from those known for ICS as a class. The efficacy of MF has been established in large, well-designed studies. Once-daily dosing has been shown to be as effective as twice daily dosing. In patients with persistent asthma on SABA alone, or on previous ICS taken twice-daily, MF has been shown to be superior to placebo in improving lung function, symptom control and quality of life. It has also allowed severe asthmatics to reduce or eliminate OCS from their regimen. MF-DPI once-daily has shown comparable or better efficacy with BDP, BUD, and FP.

Disclosures

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