EXPERT OPINION

A review of mometasone furoate/ formoterol in the treatment of asthma

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Introduction: Asthma is a common chronic respiratory disease affecting the airways causing inflammation, airway hyperreactivity (AHR), and respiratory symptoms. Frequently, asthma can be effectively treated with inhaled corticosteroids (ICS) but in more severe cases additional drugs are required, such as long-acting β2-agonists (LABA). Mometasone furoate (MF) is a synthetic steroid exhibiting a strong affinity for the glucocorticoid receptor as well as a low bioavailability and a high plasma protein binding. In most cases, MF only requires once daily administration. Formoterol fumarate (F) is a full β2-agonist with a rapid onset and 12 h of duration.
Areas covered: The present paper reviews the current knowledge of the novel combination of MF and F for the treatment of asthma. Furthermore, a description of the individual components is included.
Expert opinion: At present, only few clinical studies of MF/F are available for review and more studies of MF/F efficacy are needed, especially comparative studies on other ICS/LABA drugs. However, it does not appear from the reviewed literature that MF/F or its individual components are inferior to other equivalent treatments.

Keywords: anti-inflammatory, asthma, bronchodilation, formoterol fumarate, mometasone furoate

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1. Introduction

Asthma is a chronic inflammatory disease, characterized by airway hyperresponsiveness (AHR), airway inflammation and respiratory symptoms in the form of coughing, wheezing breath, dyspnea, and chest tightness. Asthmatic symptoms can be triggered by many different factors, including airway exposure to allergens such as pollen, dust mite feces, animal dander and fungi, but also by physical exercise and unspecific irritants such as air pollution, humidity, perfume and tobacco smoke. Asthma is very common with an estimated global prevalence of 300 million people [1]. The frequency of asthma varies considerably between countries, from 1% of a population to 18% [2]. In the future, increased incidence rates of asthma can be expected in developing countries due to better diagnostic possibilities as well as adoption of a more modern lifestyle, including urbanization [2], whereas asthma frequency in developed countries in Europe and North America in general has reached a more stable level. The severity of asthma also shows a high degree of heterogeneity. About half of the patients in most countries are classified with intermittent disease, and the proportions of patients with persistent asthma are equally distributed in the three categories of mild, moderate and severe disease [3]. In the more severe cases, asthma exacerbations can result in acute hospitalization due to respiratory failure, sometimes with a fatal outcome. As many as 255,000 people died from asthma in 2005, mostly in lower income countries [1].

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Box 1. Drug summary.

Drug name (generic)	Mometasone furoate/formoterol fumarate
Phase	IV
Indications	Persistent asthma Mometasone component: Persistent asthma Allergic rhinitis Dermatological conditions Formoterol fumarate component: Persistent asthma, added to ICS COPD
Pharmacology description/ mechanisms of action	Mometasone furoate component: Synthetic steroid; anti-inflammatory Formoterol fumarate component: β2-receptor agonist; bronchodilation through airway smooth muscle relaxation
Route of administration	Topical, inhalation
Chemical formula	Mometasone furoate component: 9,21-dichloro-11(Beta),17-dihydroxy-16 (alpha)-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) Formoterol fumarate component: (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate 40
Pivotal trials	[30-35]

The immunological mechanisms of asthma are primarily dominated by the Th2-pathway [4], with airway eosinophilia, mast cell infiltration of the airway wall and smooth airway muscle, driving the airway inflammation, AHR and in some cases persistent airflow limitation, which cause the classic asthma symptoms such as shortness of breath, wheezing and cough. Hence, cornerstone asthma treatment addresses both eosinophilic airways inflammation and AHR. In addition, a leukotriene antagonist (LTRA) which inhibits leukotrienes from the degranulation of mast cells can improve the asthmatic AHR, especially in patients with exercise or aspirin-induced asthma.

Not all asthma patients express airway eosinophilia. A non-eosinophilic asthma phenotype has thus been described, and it is found more frequently in smokers. Importantly, patients with non-eosinophilic asthma have an attenuated response to inhaled corticosteroids (ICS) and may need other treatment options.

International guidelines on asthma management recommend adjustment of asthma treatment in accordance with the degree of day and night symptoms, limitations of physical activity, need for rescue medicine and a lung function measurement [5]. For patients with mild intermittent disease, treatment with short-acting β2-agonists (SABAs) is recommended as monotherapy (GINA guidelines, step 1 [5]), whereas more persisting disease necessitates daily usage anti-inflammatory treatment with either ICS or LTRA. If disease control is not achieved, a long-acting β2-agonist (LABA) can then be added to treatment. The combination of ICS and LABA has been shown to have the advantage of a steroid-sparing effect, in that a similar degree of disease control is achieved with a given dose of ICS combined with LABA, compared to a double dose of ICS as monotherapy.

The beneficial effects of ICS in combination with bronchodilators in asthma treatment are well documented [6,7]. A possible explanation for this is the reversing effect of corticosteroids on β2-receptor desensitization, upregulating β2-receptor gene expression. Furthermore, the combination of β2-agonists and corticosteroids has been shown to facilitate the translocation of the glucocorticoid receptor from the cytosol to the site of action, the cell nucleus, increasing glucocorticoid potency.

However, the proportion of patients with an unsatisfactory degree of asthma control is still large, and there is therefore a need for new treatment options for this large group of patients. One important area of potential improvement in disease management could be treatment adherence, which unfortunately is rather suboptimal in asthma patients [8]. Most inhalator devices for persisting asthma require twice-daily administration. Usage of drugs with a longer duration of action permitting a reduction to a single daily administration might improve treatment adherence, due to increased convenience for the patients.

The aim of the present paper is to review the current knowledge of the relatively novel combination of mometasone furoate (MF, an ICS), and formoterol fumarate (F, a LABA) in the treatment of asthma.

2. Overview of the market

Several combinations including LABA and ICS are commercially available, both in separate devices and in fixed combination inhalator devices. The MF/F combination was approved in the US in 2010 [9].

For LABAs, the most frequently applied drugs are F, salmeterol, bambuterol (a pro-drug of the short-acting terbutaline)

and the relatively recently developed drug indacaterol, which excels in being a 24-h-acting LABA (supraLABA) and thus only requires once daily administration. Furthermore, arformoterol (which is a purified (R,R)-enantiomer of formeterol, see below) is available. Arformoterol and indacaterol are at present only indicated for COPD treatment. All of the drugs are effective bronchodilators, but with different potency. Generally, the most frequent side-effects overlap, with the exception of indacaterol, which has a few additional common side-effects.

For ICSs, the most significant drugs are beclomethasonedipropionate, fluticasone propionate, budesonide, ciclosonide (a small-particle agent), and MF. Recently, fluticasone furoate has been developed as a 24-h acting agent and appears promising in asthma treatment [10-12]. Most agents are available in an inhalable spray formula as well as dry powder. Generally, ICSs are effective, well tolerated and with low to moderate side-effects. There are differences in potency as well as side-effect profiles between the drugs, but what they all share is the risk of oral candidiasis (~ 5%) and potential dose-dependent systemic effects [13], for example, hypothalamic–pituitary–adrenal axis suppression [14,15] and long-term bone mineral density loss, although the latter is not securely documented in MF treatment, since study results are diverging in asthma patients [16,17]. There are however important differences in bioavailability between the drugs and thereby in the risk of systemic side-effects.

3. Formeterol fumarate

Formeterol fumarate is a long-acting selective β2-adrenergic full agonist used for the treatment of obstructive airway diseases, acting through bronchial muscular relaxation. For respiratory diseases, F is administered topically in the airways, either as dry powder inhalation or as metered-dose inhalation. The therapeutic doses of F range from 4.5 g to 18 μg daily (but up to 54 μg in extreme cases), depending on symptom severity.

3.1 Chemistry

Formoterol fumarate has a molecular weight of 840.9 Da. The empirical formula is $(C_{19}H_{24}N_2O_4)_2{\cdot}C_4H_4O_4{\cdot}2H_2O$ [9]. F consists of a relatively lipophilic molecule formulated as the fumerate dihydrate salt [18], which is a mixture of the (R,R)-enantiomer and the (S,S)-enantiomer. These are stereoisomers of the same drug.

3.2 Pharmacodynamics

F acts via the β2-receptor, which is situated in smooth airway muscle cellular membrane, with some parts of the molecule intra- and extracellularly. When stimulated, it increases intracellular cyclic adenosine monophosphate (cAMP) concentration by activating the enzymatic activity of adenylyl cyclase, which catalyses the conversion of adenosine triphosphate to cAMP. This process leads to relaxation of the smooth airway muscle tone by inactivation of the myosin light kinase enzyme. Furthermore, cAMP inhibits intracellular calcium release and thereby attenuates the contractability of the muscle [19]. In addition, formoterol inhibits the release of histamine and leukotrienes from the mast cells [20], thus further reducing the asthmatic AHR. When inhaled, F induces bronchodilation in a dose-proportional manner within a few minutes following inhalation [21,22], after which the bronchodilator effect peaks 2 h later [21]. The total duration of action is long, about 12 h; this property may be attributed to the lipophilicity of the molecule, which enables a tighter, longer-lasting binding to the receptor [19]. In contrast, SABAs are more hydrophilic in their molecular structure. In high inhalation doses, F also has cardiovascular effects in terms of increased heart rate and decreased blood pressure [21]. The (R,R) enantiomer is primarily the pharmacodynamically active [23,19] and the distribution between (R, R) and (S,S) enantiomers in formoterol fumarate solutions is roughly 1:1 [19].

3.3 Pharmacokinetics and metabolism

After inhalation, plasma concentration shows a biphasic peak within 1.58 h, and the half-life ($t_{½}$) is 1.7 – 3 h [21]. Orally administered, the half-life is 3.4 h [21]. Metabolism occurs by glucoronidation of the drug in the liver, in part via O-demethylation. This process is catalyzed by the CYP450 isoenzymes [9]. Fifteen to 28% of the inhaled dosage is excreted in urine, lowest in children [9] and biliary clearance may also contribute to the elimination [23]. The binding of formoterol to plasma proteins has *in vitro* been estimated to be 61 – 64%.

3.4 Clinical efficacy

In asthma patients, F has been shown to be efficacious on lung function and on the degree of symptoms as well as the need for emergency medication over the short and long term [21]. In comparison with salmeterol, F is associated with greater positive effects on the asthmatic airflow variation [21], lung function, symptom-free days, and need for emergency medication [6]. This may be due to the fact that salmeterol is a partial β2-agonist, as opposed to formeterol. LABA in monotherapy is not indicated in asthma according to international guidelines, due to reports of increased mortality in asthma patients treated with a LABA without ICS [19]. This may relate to a desensitization of β2 receptors, leading to development of tolerance and increased β2-agonist demand as well as to interracial β2-receptor polymorphisms affecting drug efficacy in some patient subpopulations leading to a lower response to the same dose of the drug [19].

4. Momethasone furoate

MF is a synthetic corticosteroid agent used in the treatment of dermatological diseases, allergic rhinitis and asthma, inhibiting the pathological autoimmune responses. For asthma,

MF is administered topically in the airways. The therapeutic dose range is 200 – 800 µg daily.

4.1 Chemistry

The molecular weight is 521.4 Da and the empirical formula is $C_{27}H_{30}CI_2O_6$ [9]. The steroidal D-ring in the molecule is modified compared to other steroids; this enables enhanced glucocorticoid receptor affinity [16]. Like other steroids, momethasone furoate is a lipophilic molecule, a property that allows passive transport of the molecule through the cellular membrane.

4.2 Pharmacodynamics and metabolism

Glucocorticoids acts via the glucocorticoid receptor which resides in the cytoplasm. There are several isoform subtypes of the receptor that have different capabilities of regulating the transcriptional activity on the DNA [24]. The balance between these subtypes may contribute to differences in corticosteroid responses. When activated, the glucocorticoid receptor inhibits transcription of multiple different inflammatory genes [24,25]. This happens in part through activation of the histone deacetylases which wrap DNA around the core histones, preventing transcription [26]. In this manner, glucocorticoids inhibit the secretion of asthmatic interleukins such as IL-4 and IL-5. In addition, they block the recruitment of eosinophils into the airway submucosa [16], and enhance eosinophil apoptosis [27]. Glucocorticoids also attenuate vascular cell adhesion [27] and thus inhibit the recruitment of immunological cells to the airway tissue from the circulation. Furthermore, MF also has a downregulating effect on fibroblast DNA synthesis, reducing the airway tissue remodeling that is an important feature of asthma, which may lead to a chronic reduction in lung function [16]. MF exhibits a very high affinity for the glucocorticoid receptor, which is one explanation for the high potency compared to other steroid drugs. The relative receptor affinity in human monocytes has been defined according to the affinity of dexamethasone (index = 100). For MF, this value has been measured to be 2200, which is a little more than that of fluticasone (1,800) but considerably higher than budesonide (935) and vastly superior to beclomethasone (53) [28,29].

4.3 Pharmacokinetics

After inhalation, MF is deposited in the airway and lung tissue, where the high affinity for the glucocorticoid receptor leads to a fast tissue adsorption. However, compared to fluticasone, MF has a slightly higher dissociation rate, resulting in increased desorption into plasma [28]. In addition to the deposition of inhaled steroids at the site of action, i.e., the respiratory tract, a large proportion of the inhaled drug (50 – 90%) is swallowed and thereby accesses the systemic circulation through the gastrointestinal tract [29]. Due to side-effects, high systemic bioavailability is an unwanted but important feature of ICS treatment. The oral systemic bioavailability of MF was initially estimated to be under 1% [28,29], equivalent to fluticasone and ciclesonide, and much lower than that of other agents such as beclomethasone and budesonide (15 – 26% and 11%, respectively). However, a more recent estimation was 5.3% [17] and because of transformation into active metabolites, the exact actual clinical relevant oral bioavailability of MF is not known [29]. Protein binding of MF in plasma is 98%; this relatively high value, similar to other ICS that have a binding to protein of 71 – 99%, can be considered as an advantage because only the non-bound corticosteroids are pharmacodynamically active [29]. The $t_{½}$ of MF is 4.5 h, a little higher than that of most other steroids, but lower than that of fluticasone (14.4 h) [29]. When taking systemic side-effects into consideration in regard to inhaled steroids, a short plasma half-life is attractive as opposed to a longer clearance in the airway and lung tissue. Clearance from the plasma occurs primarily in the liver [29].

4.4 Clinical efficacy

The therapeutic efficacy of MF vs placebo has been demonstrated in patients receiving SABA monotherapy or ICS prior to study enrolment, as well as in severe asthma [17]. In comparison with budesonide, fluticasone and beclomethasone, the clinical efficacy of MF has been shown to be at least similar [17].

5. Momethasone furoate/formeterol combination

The combination of an ICS and a LABA is the appropriate treatment when the asthmatic activity cannot be contained with ICS monotherapy [5]. Combination treatment with ICS and LABA has the advantage of attenuating both the causative inflammatory pathology and the bronchospasm, leading to increased asthma control, lung function improvement and exacerbation risk reduction [6,7]. The molecular and pharmacological properties as well as the clinical indications of the MF/F combination are listed in the drug summary **Box 1**.

In the recent years the combination of MF and F has been evaluated for clinical efficacy, safety and tolerability. A listed summary of the reviewed studies appears in **Table 1**.

In a 26-week study of 781 patients on medium-dose ICS evaluating MF/F vs individual components, it was shown that MF/F 200/10 µg twice daily improved FEV1 area under the curve $(AUC)_{0\text{-}12\ h}$, A.M. PEF and ACQ score more than either M, F or placebo. Correspondingly, asthma deterioration probability was reduced in the MF/F treatment group, but only significantly vs F and placebo [30].

MF/F in the doses of 200/10 µg, 400/10 µg twice daily for 12 weeks has also been evaluated comparatively with M 400 µg twice daily in high-dose ICS-treated patients [31]. Both high-dose and low-dose MF/F were superior to M monotherapy in the most important clinical parameters such as FEV1 $AUC_{0\text{-}12\ h}$ and overall asthma control (ACQ, A.M. PEF, rescue medication use and nocturnal symptoms).

In another comprehensive study focusing on efficacy outcome, it was shown that a 26-week treatment with the

Table 1. Studies of MF/F vs individual components or other ICS/LABA combination drugs.

Authors and year	Study duration and aim	N	Patient characteristics	Study arms	Main findings
Nathan et al. 2010 [30]	26 weeks Efficacy and safety	781	Patients with persistent asthma receiving medium-dose ICS	MF/F 200/10 μg b.i.d. MF 200 μg b.i.d. F 10 μg b.i.d. Placebo b.i.d.	MF/F improved lung function, ACQ and A.M. PEF vs other arms. Deterioration probability NS between MF/F and M
Weinstein et al. 2010 [31]	12 weeks Efficacy and safety	728	Patients with persistent asthma receiving high-dose ICS	MF/F 200/10 μg b.i.d. MF/F 400/10 μg b.i.d. MF 400 μg b.i.d.	Both combinations superior to M in improvement of lung function and asthma control
Maspero et al. 2010 [34]	52 weeks Long-term safety	404	Patients with persistent asthma receiving medium or high-dose ICS	MF/F 200/10 μg b.i.d. MF/F 400/10 μg b.i.d. FP/S 250/50 μg b.i.d. FP/S 500/50 μg b.i.d.	Safety profile similar between arms
Meltzer et al. 2011 [32]	26 weeks Effect on asthma deteriorations and lung function	746	Patients with asthma receiving low-dose ICS	MF/F 100/10 μg b.i.d. MF 100 μg b.i.d. F 10 μg b.i.d. Placebo b.i.d.	MF/F reduced asthma deterioration incidence, delayed time to deterioration and increased mean PEF vs other arms
Wyrwich et al. 2011 [33]	26 weeks, Phase III Evaluation of ACQ psychometric properties and predictors	1509	Patients with asthma receiving low- or medium-dose ICS	Low-dose: MF/F 100/10 μg b.i.d. MF 100 μg b.i.d. F 10 μg b.i.d. Placebo b.i.d. High-dose MF/F 200/10 μg b.i.d. MF 200 μg b.i.d. F 10 μg b.i.d. Placebo b.i.d.	MF/F improved ACQ compared to other arms in the medium-dose group
Bernstein et al. 2011 [35]	12 weeks Efficacy	722	Patients with asthma receiving medium-dose ICS alone or with LABA	MF/F 200/10 μg b.i.d. FP/S 250/50 μg b.i.d.	Similar lung function improvement, ACQ and AQLQ between arms but more rapid onset with MF/F

b.i.d: Twice daily; F: Formoterol; FP/S: Fluticasone propionate/salmeterol; MF/F: Mometasone furoate/formoterol; MF: Mometasone furoate; N: Number of patients at baseline.

combination of MF/F 100/10 μg was more beneficial on disease parameters such as deteriorations and PEF than MF or F in monotherapy [32].

Differences in ACQ improvement in MF/F vs individual components (MF and F) and placebo have also been found in a very large study of two Phase III trials [33]. It was shown that patients with persistent asthma receiving pre-study medium-dose ICS had a benefit on ACQ score improvement in the MF/F group compared to the individual components and placebo. This was not found in the low-dose ICS-stratified patients, where there were only significant differences between the MF/F and F or placebo. Importantly, the main objective of this study was not treatment efficacy on ACQ improvement but a psychometric evaluation of the ACQ tool and ACQ score predictor analysis.

In another study of fixed combination MF/F 200/10 and 400/10 μg twice daily administered with an MDI inhaler vs individual components of MF and F as well as fluticasone and salmeterol, it was shown that the safety profile of 52 weeks of treatment was similar for the different treatment arms [34]. In the same study, the treatment with MF/F exhibited the same efficacy on asthma symptoms and respiratory function as a treatment with fluticasone and salmeterol. However, the study was not designed for efficacy measurements.

The only comparative efficacy study of MF/F vs other ICS/LABA drugs that we were able to identify was a study of MF/F 200/10 μg twice daily compared with fluticasonepropionate/salmeterol (FP/S) 250/50 μg twice daily. The non-inferiority of MF/F was demonstrated in this large 12-week study [35]. In addition to a similar effect of MF/F vs FP/S on FEV1 $AUC_{0\text{-}12\ h}$ and ACQ and AQLQ improvements, it was also shown that MF/F had a more rapid onset in terms of significant bronchodilatation after only 5 min (vs 30 min for FP/S). This latter finding corresponds well to the known pharmacodynamics of F vs S.

6. Conclusion

Fixed combination of MF and F in the same inhaler devices is a fairly new advance in asthma treatment. Consequently, only few clinical evaluations comparing MF/F to equivalent treatments have yet been performed. Thus, much of our empirical knowledge is based on studies of the individual components, MF and F. MF is a potent agent due to the high glucocorticoid receptor affinity and a high plasma protein binding. Thus, the active systemic bioavailability is low, but the exact overall systemic adsorption of all metabolites is not known. However, it can reasonably be assumed that systemic effects of MF will still be lower than those of budesonide and beclomethasone due to the differences in pharmacological profile, whereas fluticasone and ciclesonide may be equal or superior in this context. The clinical efficacy, measuring lung function and symptoms, among the ICS products on the market does not differ significantly, although little is known about the comparative effect on airway inflammation. F is a full β2-agonist as opposed to the most significant other treatment choice, salmeterol. This results in some clinical efficacy superiorities over salmeterol, and enables lower dosages with similar bronchodilatatory effects. In terms of the degree of adverse effects, the MF/F combination is not significantly different from other combinations. The qualities of symptoms vary more, primarily due to the MF adverse effect profile. Therefore, treatment guided by the patient's preference and the individual clinical outcome may be the most appropriate treatment strategy.

7. Expert opinion

At present, only few clinical studies of MF/F are available for review and more studies of MF/F efficacy are needed, especially comparative studies involving other ICS/LABA drugs. However, it does not appear that MF/F or the individual components are inferior to other equivalent treatments. A potential advantage of MF/F is the duration of action, which in many cases will allow once-daily administration only, as opposed to other ICS/LABA combinations. This is a clinical advantage that many physicians and patients will appreciate.

The principles of MF/F treatment are not novel in asthma treatment. Thus overall, asthma treatment guidelines will not be influenced by the possibility offered by the MF/F combination. In a 5-year perspective, the MF/F combination will most likely be an important part of the ICS/LABA market. However, future combination drugs including a supraLABA may constitute a competitive alternative.

Declaration of interest

The authors state no conflict of interest and have received no payment in the preparation of this manuscript.

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