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Review

A valid option for asthma control: Clinical evidence on efficacy and safety of fluticasone propionate/formoterol combination in a single inhaler☆

M. Latorre [a], P. Paggiaro [a, *], W. Canonica [b], M.P. Foschino [c], A. Papi [d]

[a] Cardio Thoracic and Vascular Department, Pathophysiology Unit, University of Pisa, Italy
[b] Allergy & Respiratory Diseases, IRCCS S. Martino-University Hospital-IST, Genoa, Italy
[c] Institute of Respiratory Disease, Department of Medical and Occupational Sciences, University of Foggia, Italy
[d] Department of Clinical and Experimental Medicine, University of Ferrara, Italy

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ABSTRACT

A good level of asthma control improves the quality of life of asthmatic patients and may prevent future risk in term of exacerbations and decline of pulmonary function. However, in a real-life setting, several factors contribute to generally low compliance to the treatment. A rapid-onset, long-lasting medication with few adverse effects may contribute to improve adherence to therapy, along with an effective patient education and a good physician-patient communication. Many clinical studies demonstrated the comparable efficacy of the new fluticasone propionate/formoterol (FP/F) combination in a single inhaler to other combinations of inhaled corticosteroids and $\beta_2$agonists and the superiority of FP/F as compared to its individual components. Also the safety profile of this combination was encouraging in all studies, even at higher doses. By effectively and safely targeting both airway inflammation and smooth muscle dysfunction, the two pathological facets of asthma, and allowing the patient to adapt dose strength, FP/F combination in a single device represents a valid option to improve asthma control in patients with different levels of asthma severity.

Contents

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* Corresponding author. Cardio Thoracic and Vascular Department, Pathophysiology Unit, University of Pisa, via Paradisa 2, 56124 Pisa, Italy.
E-mail address: pierluigi.paggiaro@unipi.it (P. Paggiaro).

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1. Introduction

1.1. Level of asthma control: clinical trials versus real life

According to the most recent international guidelines (Global Initiative for Asthma, GINA), the main goals of asthma management are stable asthma symptom control and future risk reduction [1]. While symptom control may be easily assessed by evaluating in the last few months patient's symptoms, use of rescue medication and limitation of daily activities, the assessment of the future risk requires a more detailed examination of the patient's characteristics that may cause a poor outcome of the disease. Markers of a potential deterioration of asthma over time and of future exacerbations are: 1) comorbidities (like upper airway disease, gastro-oesophageal reflux, obesity); 2) persistent exposure to allergens or irritants (including cigarette smoke); 3) poor adherence to the treatment; 4) reduced lung function and 5) persistent airway inflammation (as assessed by non-invasive methods) [1]. However, it has been clearly demonstrated that by reaching and maintaining asthma control the future risk, in terms of reduction of exacerbations and attenuation of decline of the forced expiratory volume in the 1st second (FEV1) is significantly reduced [2,3], with a persistent improvement of quality of life [4].

While a good asthma control may be obtained by a step-up strategy in the majority of asthmatic patients of the randomized clinical trials (RCTs), the levels of asthma control are remarkably lower in "real-life" clinical setting and dependent on the selection of patients. While the majority of patients admitted to asthma clinics may reach a good asthma control [5,6], patients covered by the general surveys frequently report the persistence of symptoms and the limitation of daily life activities due to asthma. A recent online (internet) survey performed in 3 European countries, including Italy, showed that only a fraction of the patients as low as less than **50**% defined their asthma as well controlled [7]. Poor asthma control was associated with reduced quality of life and increased costs for asthma management. Another observational study, conducted on asthma patients attending the General Practitioner (GP) clinic only to request prescription renewal and not to be a re-assessed, showed that poor asthma control, as assessed by an Asthma Control Test (ACT) score <20, was rated by almost 30% of the asthmatic patients [8].

1.2. Patient education

According to this scenario, several strategies have been developed in order to promote a more appropriate assessment and treatment of asthma and to increase patient's adherence to medical treatment as well. The approach to patient education emphasizing the value of regular treatment and appropriate life-style is as important as the decision on the best pharmacological treatment. Moreover, a good physician-patient communication, taking into account the several unmet needs reported by the patient (e.g. quick bronchodilation after the assumption of the regular treatment, or the preference to self-manage the disease by more flexible drug schedules), may considerably improve the asthma control [9].

2. The need for more effective drugs and/or strategies

Inhaled corticosteroids (ICS) are the cornerstone of asthma treatment, recommended for regular use in all symptomatic patients (Global Initiative for Asthma GINA 2014). However in a large population of these patients, asthma control is not attained by ICS alone, while a combination of ICS with other controller drugs may be required. It has been demonstrated that adding a long-acting β2-agonist (LABA) to ICS significantly improved symptoms and pulmonary functions as compared with ICS alone even at higher doses [10,11]. Furthermore, the ICS/LABA combination consistently gave better results than other drug combinations, like ICS plus leukotriene receptor antagonists. For this reason, ICS/LABA combinations at different doses of ICS represent the preferred option of treatment, from step 3 to step 5 of GINA guidelines [1].

ICS/LABA combinations have other advantages on ICS alone: ICS and LABA are effective on both components of the disease (airway inflammation and airway smooth muscle dysfunction) and on different asthma phenotypes (prominent airway inflammation versus remodelling). This complementary effect may also associate with a synergistic effect, as demonstrated by several in vitro studies and suggested by clinical data [12]. Finally, according to the definition of asthma as "a heterogeneous disease" [1], a better control of the disease may be reached by using two drugs active on different components of the disease, which may be present at different degrees among the single members of the asthmatic patient population.

Several ICS/LABA combinations in the same inhaler have been marketed for the treatment of asthma: Fluticasone/Salmeterol, Budesonide/Formoterol, Beclomethasone/Formoterol and more recently Fluticasone Propionate/Formoterol (FP/F combination). This review summarizes the main clinical data showing the efficacy and the safety of this more recent combination, which includes one of the most powerful ICS (fluticasone propionate) with a potent full beta2-agonist (formoterol). Indeed, fluticasone propionate has the greatest affinity for the CS-receptor, the longest duration of action due to its lipophilicity, and a minimal systemic bioavailability among the currently available ICS [13]. On the other hand, formoterol is a rapid-onset, long-acting β2-agonists with a clear dose–response curve [14]. An extensive review of the pharmacologic characteristics of the two single components of this new combination is reported in another manuscript [15].

Furthermore, the wide range of different dose strengths of both fluticasone propionate and formoterol (FP/F combination: **50/5**, **125/5**, and **250/10** μg) allows a range of different options according to the different levels of asthma severity. In conclusion, this combination has the potential to represent the "best combination".

3. Clinical evidence of the fluticasone propionate/formoterol combination (FP/F)

In the last few years, many studies have been published on the efficacy of the FP/F combination, comparing this new combination with the other ICS/LABA combinations.

3.1. FD/F versus individual components: efficacy and safety

In a first group of studies [16–19] the efficacy of FP/F combination was compared with the individual components (FP or F) in patients not adequately controlled by fluticasone alone. All studies were fully compliant with the regulatory requirements: randomized, parallel group, double blind studies, of 8 or 12 weeks duration, with change in pulmonary function as primary outcome and inclusion of groups of patients treated with formoterol alone or with placebo (Table 1). In all these studies the inclusion criteria were similar, although some difference in the level of asthma severity (from moderate to severe) was reported: diagnosis of asthma since 6–12 months at least, FEV_1 between 40 and 85% of predicted value, acute reversibility after salbutamol, under treatment with no or low-medium dose ICS (<**500** μg fluticasone equivalent). In one study only [19] partial or no asthma control in the run-in under