European Journal of Internal Medicine 25 (2014) 695–700

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

Fluticasone propionate/formoterol: A fixed-combination therapy with flexible dosage

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ARTICLE INFO

Article history:
Received 26 March 2014
Received in revised form 21 June 2014
Accepted 24 June 2014
Available online 19 July 2014

Keywords:
Asthma control
Asthma exacerbations
Fluticasone propionate/formoterol
Fixed-combination therapy
Single-aerosol inhaler

ABSTRACT

International guidelines describe asthma control as the main outcome of asthma management. Prevention of symptoms, improved quality of life, and reduction of exacerbations are the main components, consequently decreasing health care costs. However, many of these objectives remain unmet in real life: several surveys show that a large proportion of asthmatic patients are not well controlled despite the efficacy of current available treatment.
Several randomized controlled clinical trials indicate that combining inhaled corticosteroids and long-acting β_2-agonists, by means of a single inhaler, greatly improves the management of the disease. The results of 9 multicenter phase III clinical studies demonstrate that the fixed combination of fluticasone propionate/formoterol in a single inhaler is effective in terms of lung function and symptom control. These studies highlight the dose flexibility, safety and tolerability of this new inhaled combination. These characteristics meet the recommendations of international guidelines, and the preferences of respiratory physicians who identified these aspects as critical components of a successful asthma therapy. Combination of fluticasone propionate/formoterol in a single inhaler provides potent anti-inflammatory activity of fluticasone propionate and rapid onset of action of the β_2-agonist formoterol making this association a viable treatment option both in terms of effectiveness and compliance.

1. Introduction

Asthma affects about 300 million people of all ages and ethnic groups worldwide [1], with an estimated increase in prevalence to 400 million by 2025 [2]. The economic burden in terms of direct (hospitalization, use of emergency room visits, therapy) and indirect (missed days of work/school) costs adds to the emotional, physical and social impact of asthma, with consequent quality of life deterioration for both patients and their families [3]. Despite the availability of effective treatments, a large proportion of asthma patients experience symptoms of uncontrolled asthma, even in those geographical areas where good standards of care are available [2,4–8].

In the AIRE (Asthma Insights and Reality in Europe) study, involving over 2800 patients from different European countries, more than half of the patients reported daytime asthma symptoms and a third complained of asthma-related sleep disturbances [9]. The INSPIRE (International Asthma Patient Insight Research) study, where 3415 adults treated for asthma were interviewed, reported daily use of rescue short-acting bronchodilator in almost 74% of the patients, while 51% had experienced at least one exacerbation in the previous year [7]. More recently, in 2006, 2008 and 2010, the results of three surveys in patients from five European countries (France, Germany, Italy, Spain and United Kingdom) revealed that 50% or more of asthma patients reported suboptimal symptom multi-dose DPIscontrol [5,10,11].

2. Potential causes of inadequate asthma control

Among the possible causes of impaired asthma control, the heterogeneity of the disease, the continued exposure to irritants or triggers,

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http://dx.doi.org/10.1016/j.ejim.2014.06.022
0953-6205/

the presence of co-morbid conditions [12] and the lack of patient adherence to treatment [13] should be considered. In the last years some greater attention has been put in the diagnosis and management of co-morbidities and triggers. By contrast, non-adherence to medications remains very common in asthma, perhaps more than in other chronic diseases. Indeed, there is evidence to indicate that a combination of suboptimal use of available drugs, poor adherence to treatment and misjudgment of the level of asthma control by physicians and/or patients, contributes to unsuccessful disease control. Possibly this is also due to poor inhaler technique, a variety of unintentional non-adherence, which is widespread and neglected in asthma [14]. Two main types of inhaler devices are currently available for drug lung delivery in asthma, metered dose inhalers (MDIs) and dry powder inhalers (DPIs). Importantly, the issue of inhaler misuse was firstly recognized with MDIs, as the diffusion of DPIs is relatively recent. However, it is currently known that inhaler misuse is common with both MDIs and DPIs and is associated with poor asthma control with both devices [15]. Although it is increasingly believed that a careful choice of the most appropriate inhaler device, in accordance with the patient, can certainly improve patient's satisfaction, adherence and clinical outcomes, guidelines do not give a clear indication about the best device. In fact, it is accepted that different devices are clinically equivalent with regard to safety and efficacy when they are used to deliver the same drug at equipotent doses [16]. Similarly, there is no clear evidence for a preference between inhaler devices [17]. However, simplifying the regimen schedule, by including the use of a single inhaler with different drug combinations, or using the same type of device when different drugs are required, or the addition of bronchodilators with fast onset of action may improve asthma adherence and control. This may suggest the use of MDIs as first inhaler option in asthma. Moreover, although the price of different asthma inhaler drugs is variable between countries and depends on the agreement between manufacturers and health providers, MDIs are also cheaper than multi-dose DPIs.

Knowledge, belief and behavior of physicians are crucial elements of the management and follow-up of chronic inflammatory disorders, including asthma [18]. A recent survey conducted among general practitioners (GPs, n = 811) and respiratory medicine specialists (n = 230) investigated physician-related factors potentially contributing to asthma control failures. In this survey physicians considered 40% of asthma patients might not require continuous therapy, despite acknowledging the role of airway inflammation in the pathogenesis of disease [18]. Similar results were observed in the GAPP (Global Asthma Physician and Patient), study, a survey based on 3559 interviews in 16 countries worldwide among physicians, adult asthma patients and asthma nurses [19].

3. Goals of asthma management

The first editions of the Global Initiative for Asthma (GINA) recommendations evaluated asthma severity based on the clinical characteristics of the patients. In the following years it became increasingly evident that the evaluation of asthma severity must involve patient's response to treatment. More recently, the international recommendations suggest assessing the level of asthma control at each current patient's level of treatment. The selection of parameters for asthma control level assessment include daytime and nighttime symptoms, limitations of daily activity, impairment of lung functions, and use of rescue medications. A step-up/step-down approach is recommended to achieve these goals. This includes the dosage increase of controller medications or the introduction of another medication in those patients where asthma is not well controlled. Moreover, in cases of adequate disease control, the reduction of dosage and number of medications is recommended as well, to minimize adverse effects and health care costs [20].

The results of numerous randomized and controlled clinical studies have demonstrated the efficacy of using ICS/LABA (an inhaled corticosteroid combined with a long-acting inhaled β_2-agonist) in a single inhaler for the treatment of asthma of patients not controlled by low doses of inhaled steroids [21–26]. Moreover, it has been shown that the combination of these drugs considerably improved the management of asthma symptoms, including mild and severe exacerbations, as compared with the administration of ICS as monotherapy [27,28].

Recently, a study was performed to evaluate the characteristics of ICS/LABA combination therapy, considered by physicians as more relevant for asthma treatment. GPs and specialists from European countries were asked to complete Delphi questionnaires and to take sequential surveys. At the end of this survey, a panel of experts highlighted six main characteristics of ICS/LABA combination treatment: i) dosage flexibility (88% of attendees), ii) safety and long-term tolerability of ICS (81%), iii) safety and long-term tolerability of LABA (81%), iv) efficacy in asthma control (69%), v) anti-inflammatory power of ICS (69%), vi) rapid bronchodilator activity of LABA (68%) [Table 1] [29].

Recently, a new combination ICS/LABA became available in the market, developed with fluticasone propionate and formoterol in three dosages of 50/5 μg, 125/5 μg and 250/10 μg, respectively, per actuation.

4. Fluticasone *propionate* and formoterol

International guidelines for the management of asthma recommend the administration of a LABA along with ICS when symptoms are not well controlled using low doses of ICS monotherapy [30,31] [Fig. 1]. Combined treatment with ICS and LABA by a single inhaler has some advantages, in terms of pharmacology and compliance, compared with treatments administered separately. Indeed, it had been demonstrated that concurrent ICS and LABA can pharmacologically synergize. In clinical trials ICS/LABA combination is superior to higher doses ICS on relevant clinical outcomes [6,23,32–35], and that the use of a single inhaler improves patient adherence to therapy and ensures that the LABA is not taken as a single medication without the inhaled steroid [30,33,36,37].

The choice of ICS and LABA to be combined in the same inhaler is crucial because both ICSs and LABAs differ in terms of their specific pharmacological profiles as a result of the different chemical structures of individual agents. In the present review we only discuss ICS and LABA entering a fixed ICS/LABA combination. Fluticasone propionate is one of the most potent ICSs [35]. It has a very low oral bioavailability (≤1%) [35] and it is well accepted that low oral availability (<10%) decreases systemic availability and the incidence of adverse events [38]. High receptor binding strength is correlated with high anti-inflammatory activity [39]. The relative receptor-binding affinity (vs dexamethasone) of fluticasone *propionate* is second only to mometasone [35]; however, the inhalation half-life of mometasone is much lower than that of fluticasone *propionate* [35]. Being inhalation half-life a critical property for an ICS as it relates to pulmonary retention time (i.e. the rate at which ICSs are absorbed across the pulmonary membranes and out of the airways) [40]. This is a disadvantage for mometasone because longer pulmonary retention is related to prolonged efficacy [40]. Moreover, fluticasone *propionate* is the most lipophilically active ICS [35], and therefore has a long duration of anti-inflammatory action. In fact, higher lipophilicity is positively correlated with increased retention in the lung and longer duration of action [38].

Table 1
Expert panel agreement* on the characteristics of an effective ICS/LABA combination therapy. The results refer to the final round of a Delphi process [29].

Treatment attribute	Percentage of agreement
Dosage flexibility	88%
ICS: long term safety and tolerability	81%
LABA: long term safety and tolerability	81%
Efficacy (asthma control)	81%
ICS: anti-inflammatory effect	69%
LABA: speed of onset	69%

ICS, inhaled corticosteroid; LABA, long-acting inhaled β_2-agonist.
* Agreement = consensus in a percentage of experts ≥66%.