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Review Article

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

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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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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%.

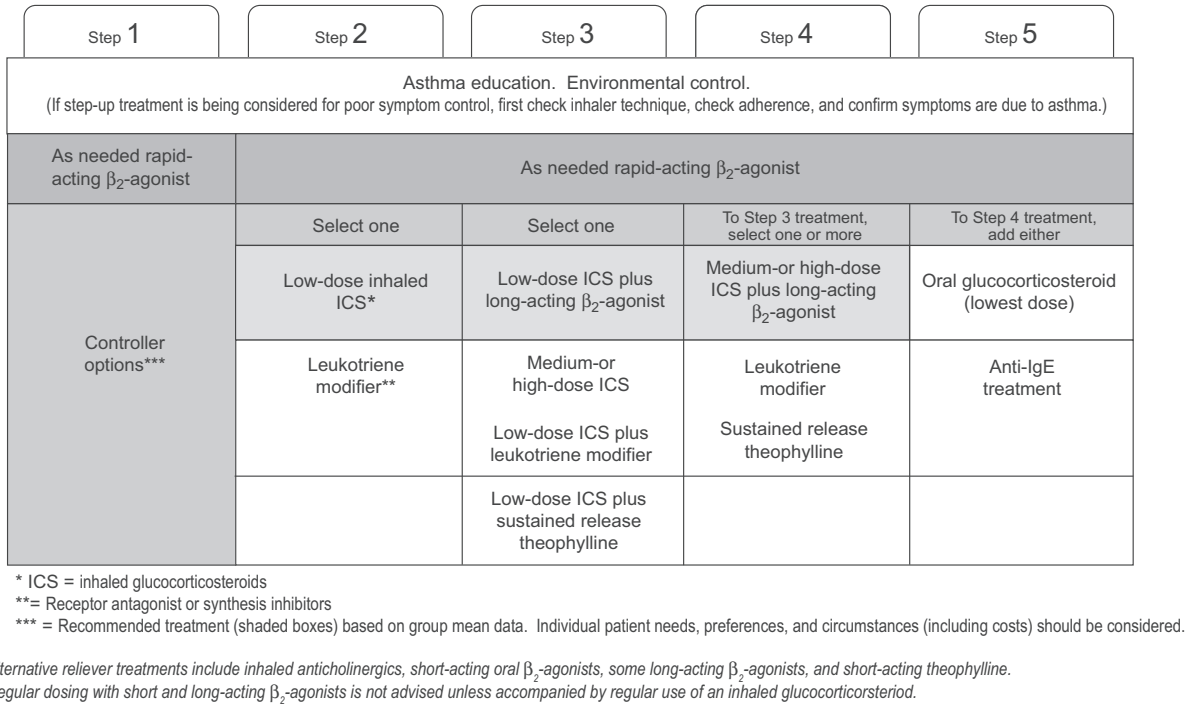

Fig. 1. Treatment steps of asthma management according to guidelines GINA (reproduced with permission) [31]. * ICS, inhaled corticosteroid. ** Receptor antagonist or synthesis inhibitors. *** Recommended treatment (shaded boxes) based on group mean data. Individual patient needs, preferences, and circumstances (including costs) should be considered.

Pharmacological characteristics that could theoretically optimize ICS effectiveness include a low oral and a high pulmonary bioavailability, high receptor-binding affinity, high protein-binding capacity and a long pulmonary retention time [38]. Important properties for a LABA include speed of onset of action, duration of action and agonist activity at the β_2-adrenoceptor [41]. Formoterol is the fastest acting inhaled LABA, considerably quicker than salmeterol [42]. The duration of bronchodilatory action of formoterol is up to 12 h, longer than that of salbutamol and similar to that of salmeterol [43]. However, the rapid onset of action supports the use of formoterol as a reliever medication in addition to use in maintenance therapy [43].

Pharmacologically, the clearest distinguishing feature between β_2-agonists is the extent to which they activate the receptor, termed intrinsic efficacy [44]. It is a key pharmacologic parameter that differs dramatically among available β_2-agonists [41]. Formoterol demonstrates high intrinsic efficacy when stimulating cyclic adenosine monophosphate (cAMP) generation, whereas salmeterol has a much lower intrinsic efficacy, appearing as a partial agonist in all but the most highly expressed recombinant systems [45]. Actually, in the maintenance setting, salmeterol has a low intrinsic efficacy (i.e., is a weak partial agonist, with intrinsic efficacy less than 2% relative to adrenaline), whereas formoterol has a relatively high intrinsic efficacy. It can be expected that more severely affected patients with asthma will show greater responses to formoterol, whereas patients having problems with side effects might do better with salmeterol [46]. Unfortunately, the degree of agonist-induced desensitization of the β_2-adrenoceptor also is related to agonist efficacy (strength of signaling), whereby high-efficacy agonists (e.g. formoterol) cause more phosphorylation and internalization of the receptor than low-efficacy agonists (e.g. salmeterol) [47].

However, high-efficacy agonists do not necessarily cause more functional desensitization, as was once believed [44]. It is known that partial agonists are generally more sensitive to the reduction of functional receptors than full agonists [44,48]. In fact, low-efficacy ligands are less able to activate the receptor and may not be sufficient to generate a full response, even when bound to all available receptors. In contrast, high-efficacy agonists may only need to occupy a small percentage of receptors to generate a full response, thereby leaving 'spare receptors' [44].

4.1. Functional benefits of combination therapy

The results of clinical studies conducted on fluticasone *propionate*/formoterol combination treatment demonstrate better efficacy in terms of improvement of respiratory function, compared with the results of the single drugs administered as monotherapy. The contribution of single components in improving respiratory function has been evaluated by assessing 1) the changes from baseline of pre-dose forced expiratory volume in 1 s (FEV_1) at week 12, when comparing fluticasone proprionate/formoterol versus fluticasone propionate, and 2) FEV1 changes from pre-dose baseline to 2 h post-dose at week 12 when comparing fluticasone propionate/formoterol versus formoterol [33–35,37,49].

A new once daily fluticasone furoate/vilanterol combination has been recently approved by regulatory agencies for the use in asthma and COPD. It confirms the superiority of ICS plus LABA over monocomponents on relevant outcomes

4.2. Therapeutic efficacy and tolerability

The therapeutic efficacy of the fluticasone *propionate*/formoterol combination has been evaluated in nine multicenter phase III clinical studies [32–34,50–55] on patients aged ≥ 12 years [32–34,50–55] or aged ≥18 years [32,33] with mild to moderate [53,54], moderate to severe [32,33,50,51,55] or mild to moderate–severe persistent asthma [34,52] [Table 2]. Further studies and pooled analyses are to be expected. The results of the published clinical studies showed that 8–12 week treatment with fluticasone *propionate*/formoterol combination in a single inhaler, at dosages of 100/10 μg b.i.d., 250/10 μg b.i.d. and 500/20 μg b.i.d., have shown superior clinical efficacy to the same doses of the single medications. Fluticasone proprionate/formoterol combination is marketed at the following dosages: 50 fluticasone proprionate/5 μg formoterol, 125 fluticasone proprionate/5 μg formoterol and 250 fluticasone proprionate/10 μg formoterol. Two puffs b.i.d. is the recommended regimen. These results were confirmed by a combined data analysis of five randomized double-blind studies, conducted in moderate or moderate–severe asthma patients, treated for 8 weeks or 12 week

Table 2
Efficacy of the combination fluticasone/formoterol for the treatment of asthma patients: results of phase III clinical studies.

Study	Asthma severity	Patient age (y)	Treatment duration (weeks)	Comparative treatment	Primary endpoint	Result of fluticasone/formoterol combination
[33]	Moderate–severe	≥18	8	Fluticasone + formoterol or fluticasone monotherapy	Morning pre-dose FEV_1 variation; morning FEV_1 pre-dose vs 2 h post-dose FEV_1	Non inferiority
[34]	Mild–moderate/severe	≥12	12	Fluticasone + formoterol	Morning pre–dose FEV_1 vs 2 h post–dose FEV_1	Non inferiority
[32]	Mild–moderate/severe	≥18	12	Fluticasone/salmeterol	Morning pre-dose FEV_1 variation	Non inferiority
[50]	Moderate–severe	≥12	12	Budesonide/formoterol	Morning pre-dose FEV_1 variation	Non inferiority
[51]	Moderate–severe	≥12	12	Fluticasone or formoterol or placebo	Morning pre-dose FEV_1 variation; morning pre-dose FEV_1 vs 2 h post-dose FEV_1; treatment discontinuation due to lack of efficacy	Superiority
[52]	Mild–moderate/severe	≥12	6–12 months	Not applicable	Safety	Safe also at long term
[53]	Mild–moderate	≥12	12	Fluticasone or formoterol or placebo	Morning pre-dose FEV_1 variation; morning pre-dose FEV_1 vs 2 h post-dose FEV_1; treatment discontinuation due to lack of efficacy	Superiority
[54]	Mild–moderate	≥12	12	Fluticasone or formoterol	Morning pre-dose FEV_1 variation; morning pre-dose FEV_1 vs 2 h post-dose FEV_1	Superiority
[55]	Not indicated	≥12	12	Fluticasone (two different formulations)	Morning pre-dose FEV_1 vs 2 h post-dose FEV_1	Superiority

FEV_1, forced expiratory volume in 1 s.

period with the fluticasone *propionate*/formoterol combination. In particular, the results of this analysis revealed that the combined administration of fluticasone *propionate*/formoterol at every available dosage (100/10 μg b.i.d., 250/10 μg b.i.d. and 500/20 μg b.i.d.) showed a statistically significant superior efficacy to the administration of single components, as evaluated by FEV_1 variations at baseline pre-dose and pre-dose at the end of the study ($p < 0.001$) [37,56]. The results of the combined analysis showed that the fluticasone *propionate*/formoterol combination in a single dose inhaler is superior to the single components, also in terms of tolerability. Moreover, patients treated with the combined therapy experienced a lower rate of exacerbations than those treated with fluticasone *propionate* (odds ratio 0.75; IC 95% 0.59–0.96) or with formoterol as monotherapy (odds ratio 0.49; IC 95% 0.34–0.70) [37,57].

Furthermore, comparative studies performed on patients treated with fluticasone *propionate*/formoterol combination in a single dose inhaler versus the single components administered concurrently have shown the non-inferiority of the combination for: 12-hours serial FEV_1 area under the curve (AUC), peak expiratory flow (PEF) in morning and evening pre-dose evaluations, asthma symptom scores, percentage of symptom-free days, quality of life (based on the Asthma Quality of Life Questionnaire, AQLQ), mean sleep disturbance scores, and number of uses of rescue medications. Additionally, the percentage of patients who were discontinued due to lack of efficacy of the therapy was lower in the group treated with the fluticasone/formoterol combination than in the group of patients who concurrently received the two medications at equivalent doses using two separate inhalers (3.9% and 7.7% respectively) [37,57]. The results of efficacy studies, conducted with the combined administration of fluticasone *propionate*/formoterol (100/10 μg b.i.d., 250/10 μg b.i.d.) with fluticasone *propionate*/salmeterol (100/50 μg b.i.d., 250/50 μg b.i.d.) have shown the non-inferiority of the former in terms of FEV_1 pre-dose baseline versus FEV_1 pre-dose at week 12 of treatment ($p = 0.007$) and of FEV_1 pre-dose baseline versus FEV_1 2 h post-dose at week 12 of treatment ($p = 0.002$), in terms of PEFR, sleep disturbance scores, rescue medication use and asthma exacerbations. These efficacy results were replicated when fluticasone *propionate*/formoterol and budesonide/formoterol combined therapies were compared [50].

The results of clinical studies comparing fluticasone *propionate*/formoterol combined therapy versus i) monotherapy with single components, ii) therapy with single components administered concurrently, iii) fluticasone *propionate*/salmeterol combined therapy, and iv) budesonide/formoterol combined therapy, showed superior efficacy for the fluticasone *propionate*/formoterol combination compared with monotherapy with single components. Moreover, fluticasone propionate/formoterol demonstrated non-inferiority to fluticasone *propionate*/salmeterol or budenoside/formoterol combinations, in terms of lung function and asthma control. However, the fluticasone/formoterol combination has a more rapid bronchodilator effect than the fluticasone *propionate*/salmeterol combined treatment, defined as the first post-dose measurement with $FEV_1 \geq 12\%$ of the corresponding pre-dose value ($p = 0.001$) [32,37]. Moreover, the fluticasone/formoterol combination is well tolerated at all considered doses [32–34,50–55], including in long-term treatments up to 12 months [52].

The clinical efficacy of an inhaler therapy is also based on the ability of the inhaler device to provide an adequate dose of medication to the lower respiratory tract. The drug particle size range is the main characteristic of the aerosol, determining rate, distribution and the deposition site of the medication inhaled by the airways. It has been demonstrated that the percentage of respirable fraction contained in the aerosol (defined as drug particles with the diameter range between 2 and 5 μm) correlates with the drug deposition in lung tissues [57,58]. The inhaler used for the administration of the fluticasone *propionate*/formoterol combination ensures the distribution of an aerosol with a respirable fraction of 40% of the inhaled dose [59], which is consistent at different inspiratory flows, with a plume value of 168 ms [60]. These characteristics facilitate drug deposition throughout the airways.

The DIFFUSE study has extensively evaluated the particle size distribution of the aerosol delivered by the fluticasone/formoterol combination inhaler at the strength of 5/125 μg in accordance with the European Pharmacopeia [59]. The mean (±SD) Median Mass Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) were respectively 3.52 (±1.59) for the LABA and 3.52 (±1.56) for the ICS at a flow of 28.3 lpm; the Fine Particle Fraction (FPF) of the labeled dose was, respectively, 39% and 41%. Further in vivo studies should confirm these results, but they suggest a good and homogeneous lung drug distribution for both drugs. Interestingly, the fluticasone propionate/formoterol combination shows good consistency in proper drug delivery at different flow rates. In fact, the FPF at 60 lpm showed percentages of 41% for the LABA and 44% for the ICS. This characteristic may be very important as fast inhalation is one of the most common

errors with metered dose inhalers in clinical practice. Poor hand-lung coordination, another common misuse of inhaler technique, may be overcome, if necessary, using a valved holding chamber. The use of AeroChamber Plus, which, possibly, may also contribute to increase lung drug deposition, is suggested into the package leaflet of the fluticasone propionate/formoterol inhaler.

The same DIFFUSE study has compared the aerodynamics of fluticasone propionate/formoterol to that of two most commonly used LABA/ICS combination inhalers, such as salmeterol/fluticasone propionate Diskus and budesonide/formoterol Turbuhaler, respectively at the estimated equipotent strengths of 50/250 and 4/160 μg. At 60 lpm, the optimal inhalation flow with both DPIs, the MMAD, GSD and FPF of labeled dose were, respectively, 4.0, 2.0 and 15% for salmeterol and 3.7, 1.8 and 18% with fluticasone propionate. The MMAD, GSD and FPF of labeled dose were 2.5, 1.9 and 30% with formoterol and 2.5, 1.9 and 35% with budesonide [59]. These results are substantially in accordance with other previously known, where the average MMAD, GSD and Fine Particle Dose of labeled dose were, respectively, 3.5, 1.5 and 18% for salmeterol and 3.6, 1.5 and 20% with fluticasone propionate using the Diskus; and 3.3, 1.6 and 11% with formoterol and 3.1, 1.6 and 13% with budesonide using the Turbuhaler [61].

5. Conclusion and discussion

According to the recommendations of international guidelines, the aim of asthma management is reaching stable and optimal symptom control, improving patient quality of life, and minimizing the exacerbation rates, with the consequent reduction of direct and indirect health care costs. However, the results of many surveys among general practitioners, respiratory medicine specialists and patients reveal that a large percentage of asthma patients under treatment still have symptoms of not well controlled disease.

Combination treatment with a LABA in addition to ICS is the mainstay of the management of asthma, when the disease is not adequately controlled by low dose ICS alone. The administration of ICS and LABA in a single inhaler provides advantages in terms of pharmacology and compliance. Indeed, the two drugs in combination synergistically enhance the pharmacological effects of the two components. Moreover, the use of a single inhaler device improves patient adherence to therapy.

The results of clinical studies conducted on the fluticasone *propionate*/formoterol combination reveal that these two medications, when administered concurrently in a single inhaler, show efficacy and are well tolerated. Symptom control and consequently quality of life of asthma patients are improved.

The pharmacological characteristics of this combination fulfill the criteria established by the main international guidelines for asthma management, allowing the dosage flexibility required by step-up and step-down therapy.

The presence of formoterol in the combination with fluticasone *propionate* allows one or two inhalations per single administration, with a wider range of ICS and LABA dosages available to the patients. Moreover, the combination of fluticasone *propionate* and formoterol shares the most relevant characteristics of ICS and LABA respectively, recommended by physicians for effective asthma management.

To date, available data suggest that the combination of the anti-inflammatory effects of fluticasone *propionate* and the rapid acting bronchodilator effects of formoterol provides a valid treatment option for asthma, from the point of view of both therapeutic efficacy and patient compliance.

The combination of fluticasone *propionate* ICS and formoterol LABA in a single inhaler for asthma treatment of adults (aged ≥12 years) provides a valid therapeutic option in terms of efficacy, patient adherence to treatment and compliance to the recommendations of international guidelines.

Learning points

- The aim of asthma management is a stable and optimal symptom control, to minimize exacerbation rates and improving patient quality of life.
- In a large percentage of asthma patients disease is not controlled even if under treatment.
- The combination therapy with a LABA and ICS in a single inhaler allows one or two inhalations per single administration, providing pharmacological and compliance advantages.
- The combination of anti-inflammatory fluticasone and rapid-acting bronchodilator formoterol in a single inhaler shows efficacy and is well tolerated, fulfilling the International Guidelines Criteria.

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Conflict of interest statement

–A. Papi gave presentations at symposia sponsored by, received from or served on scientific advisory boards of Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Dompè, GSK, Guidotti, Menarini, MSD, Mundipharma, Novartis, Pfizer, Takeda, TEVA, and Zambon.

–F. Blasi served as advisory board member or received lectures honoraria or research grants from AstraZeneca, Almirall, Bayer, Boehringer Ingelheim, Chiesi, Dompè, GSK, Guidotti-Malesci, Menarini, Mundipharma, Novartis, and Zambon.

–G.W. Canonica served as advisory board member or received lectures honoraria from AstraZeneca, Almirall, Boehringer Ingelheim, Chiesi, GSK, Guidotti-Malesci, Lallemand, Meda, Menarini, Mundipharma, Novartis, Recordati, and Uriach.

–M. Cazzola has received honoraria for speaking and consulting and/or financial support for attending meetings from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Dey, GlaxoSmithKline, Lallemand, Menarini Farmaceutici, Mundipharma, Novartis, Pfizer, Sigma Tau, and Takeda.

–S. Centanni reports having received lecture fees from: Pfizer, Novartis, GSK, Mundipharma, Angelini, Almirall, Boehringer Ingelheim, and Chiesi Farmaceutici.

–M.P. Foschino received lecture fees from Mundhipharma, Guidotti-Malesci, Almirall, and Astra Zeneca

–A.S. Melani has served as an advisory board member, has been reimbursed for speaker honoraria, and has received fees as a consultant from Chiesi, Menarini Farmaceutici, Novartis, Mundipharma, GSK, Sanofi-Aventis, Almirall and Artsana.

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