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Review

Differences in the efficacy and safety among inhaled corticosteroids (ICS)/long-acting beta2-agonists (LABA) combinations in the treatment of chronic obstructive pulmonary disease (COPD): Role of ICS

M. Latorre [a], F. Novelli [a], B. Vagaggini [a], F. Braido [b], A. Papi [c], A. Sanduzzi [d], P. Santus [e], N. Scichilone [f], P. Paggiaro [a, *]

[a] Cardio-Thoracic and Vascular Department, Pathophysiology Unit, University of Pisa, Italy
[b] Allergy and Respiratory Diseases Clinic, DIMI, University of Genoa, IRCS AOU San Martino-IST, Genoa, Italy
[c] Respiratory Medicine, Department of Medical Sciences, University of Ferrara, Ferrara, Italy
[d] Section of Respiratory Diseases, Department of Surgery and Clinical Medicine, University of Naples, Italy
[e] Dipartimento di Scienze della Salute, Pneumologia Riabilitativa Fondazione Salvatore Maugeri, Istituto Scientifico di Milano-IRCCS. Università degli Studi di Milano, Italy
[f] Department of Internal Medicine, Section of Pulmonology (DIBIMIS), University of Palermo, Palermo, Italy

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ABSTRACT

Inhaled corticosteroids (ICS) are frequently recommended for the treatment of asthma and COPD, often in combination with long-acting beta2-agonists (LABA), depending on the severity of the disease and/or on the specific phenotype. Several ICS/LABA combinations are currently available that differ in their pharmacokinetic characteristics and dose of both components. Thus, this review assesses differences in the efficacy and the safety profiles of the ICS components in the two more frequently used ICS/LABA combinations (budesonide/formoterol and fluticasone/salmeterol) for the management of COPD.

Whereas the basic mechanism of action is similar for all ICS (binding with the intracellular glucocorticoid receptor, which mediates both genomic and non genomic effects), the pharmacokinetic and characteristics of ICS are quite different in terms of receptor affinity, bioavailability, lipophilicity and drug persistence in the airways. Fluticasone persists longer in airway mucus and requires more time to dissolve in the lining fluid and then enter the airway wall, whereas budesonide is cleared more quickly from the airways.

Comparative efficacy of the two major ICS/LABA combinations recommended for the treatment of COPD show similar efficacy in terms of reduction of exacerbations, improvement in forced expiratory volume in the first second (FEV1) and quality of life. One retrospective cohort study suggested a greater efficacy for the budesonide/formoterol combination on hospital or emergency department admissions, oral corticosteroid courses, and addition of tiotropium, and an observational real-life study reported a greater reduction of COPD exacerbations with budesonide/formoterol than with fluticasom/salmeterol combination.

Among the potential side effects of chronic ICS treatment in patients with COPD, recently the use of fluticasone or fluticasone/salmeterol combination has been associated with a higher prevalence of pneumonia in the major long-term studies. On the other hand, no similar increased risk of pneumonia has been reported in patients with COPD treated with the budesonide/formoterol combination. A recent population-based cohort study from the Quebec database showed that the adjusted odds ratio for having severe pneumonia was higher for fluticasone (2.1) than for budesonide (1.17) or other ICS (1.41). Of the ICS studied, only fluticasone demonstrated a dose-related increase in risk of pneumonia in patients with COPD. This difference between fluticasone and budesonide may be explained by the longer retention of fluticasone in the airways, with potentially greater inhibition of type-1 innate immunity.

Therefore, the risk:benefit ratio should be evaluated thoroughly when choosing an ICS/LABA combination for patients with COPD.

* Corresponding author. Cardio-Thoracic and Vascular Department, University Hospital of Pisa, Via Paradisa 2, 56124 Pisa, Italy. Tel.: +39 050 995365; fax: +39 050 580124.
E-mail address: pierluigi.paggiaro@unipi.it (P. Paggiaro).

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1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are major diseases, both in terms of their prevalence in the general population and the associated socio-economic burden. Those are characterized by variable degrees of airway obstruction, and the two diseases involve underlying inflammation of the bronchial wall and lung parenchyma that differ in terms of their characteristics and response to treatment.

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory agents used to treat airway diseases, because of their role in modifying several inflammatory cells and pathways involved in asthma and COPD [1]. In asthma, ICS are the cornerstone of pharmacologic treatment, and are recommended in all symptomatic patients, at doses that differ depending on disease severity, as monotherapy or in combination with long-acting beta2-agonists (LABA) or leukotriene receptor antagonists [2]. In COPD, ICS represent a second step treatment, and those are in general recommended in more severe patients (FEV1 $\leq$ 50% of predicted), who remain symptomatic despite long-acting bronchodilator treatment, and/or patients with frequent exacerbations [3]. Recently, a special clinical and functional situation, characterized by features typical of both asthma and COPD (asthma-COPD overlap syndrome, ACOS) has been described and well characterized in terms of diagnosis and treatment; ICS, together with long-acting bronchodilators, are recommended for treating these patients [4].

Currently, several ICS/LABA combinations are available: the older fluticasone propionate/salmeterol (FS) and budesonide/formoterol (BF) combinations, and the more recent beclometasone/formoterol (BDP/F), fluticasone propionate/formoterol (FF), and mometasone/formoterol (MF) combinations. While the first two combinations are indicated for treatment of both asthma and COPD, the others are now recommended only for treating asthma. Furthermore, also fluticasone furoate/vilanterol (FV) combination has been introduced on the market, with the indication for COPD treatment in US only, but very limited data are available with this combination.

Despite sharing a similar basic mechanism of action, ICS differ in terms of pharmacokinetic characteristics, and this may determine important difference in their efficacy and safety. Therefore, an important question is whether all ICS are equivalent in the management of airway diseases. Very few comparative studies have been conducted, and only indirect comparisons are available.

This review will attempt to understand if there are differences in the efficacy and in the safety profiles of the ICS included in the ICS/LABA combinations currently used for the management of COPD. In particular, the aim of this review was to compare the two more frequently used ICS/LABA combinations in COPD patients (budesonide/formoterol and fluticasone/salmeterol) in terms of efficacy (reduction in the rate of exacerbations) and of safety, with special attention to the risk of pneumonia.

2. Pharmacology of inhaled corticosteroids

Corticosteroid (CS) effects on target cells are mediated by mechanisms that involve binding to DNA, or mechanisms that are independent of DNA binding [5]. The genomic effect of corticosteroids occurs through binding of the CS molecule to cytoplasmic glucocorticoid receptors (GR), after which the CS-GR complex enters the nucleus and interacts with specific steroid-responsive DNA sequences, leading to *trans-activation* of genes encoding transcription factors that promote the release of anti-inflammatory compounds (e.g., lipocortin) and to downregulate the release of pro-inflammatory cytokines. This activity of the CS-GR complex requires activation of histone-deacetylase (HDAC), which changes the local chromatin structure and de-represses transcription of nuclear sequences, allowing them to be transcribed. Whereas, the effect of CS independent of direct DNA binding is due to the ability of the CS-GR complex to bind certain signal-dependent transcription factors (e.g., nuclearfactorkB (NFkB), activator protein 1 (AP-1)) that are normally activated as a result of signal transduction cascades originating from the binding of circulating cytokines to specific cell receptors. Binding of these transcription factors by CS-GR neutralises their ability to transactivate genes encoding pro-inflammatory molecules (*trans-repression*). The intrinsic binding activity of a CS for the GR is the main determinant of its efficacy for both of these mechanisms; however, other pharmacokinetic characteristics (e.g., solubility, retention in the cell, rate of inactivation) are also important.

In Table 1 are reassumed the pharmacokinetic and pharmacodynamic characteristics of the available ICS, data extensively reviewed elsewhere [6–9]. Binding affinity for the GR is particularly high for fluticasone and mometasone, followed by budesonide and by other ICS. Systemic bioavailability is negligible for fluticasone, mometasone and ciclesonide, but it is also low for budesonide, whereas it is high for beclometasone and flunisolide. The volume of distribution is large for fluticasone and ciclesonide, due to their high liposolubility, intermediate for budesonide, mometasone, and beclometasone, and low for flunisolide. The binding affinity, combined with the percent of lung delivery obtained with the various formulations (metered-dose inhalers, MDI, vs dry powder inhalers, DPI) available for the different compounds, allows calculation of the equivalent doses of each ICS. These data are available in several equivalence tables, for example, in the international GINA guidelines. For the most frequently used ICS (included in ICS/LABA combinations) for the treatment of asthma and COPD, 400 mcg of beclometasone in a hydrofluoroalkane (HFA)-propelled pressurised metered-dose inhaler (pMDI) is equivalent to 800 mcg of DPI budesonide and to 500 mcg pMDI/DPI fluticasone [2].

Currently only fluticason/salmeterol and budesonid/formoterol combinations are licenced for the treatment of COPD, therefore, we will continue with a pharmacologic comparison of fluticasone and budesonide. As mentioned before, fluticasone has higher intrinsic affinity and lower systemic bioavailability than budesonide. However, the most important difference between these two compounds is the higher lipophilicity (log K) of fluticasone (log $K = 4.5$) versus that for budesonide (log $K = 3.7$). This may explain the larger volume of distribution of fluticasone. Another important difference is

Table 1
Determinants of efficacy and therapeutic index in the different ICS (adapted with permission from Raissay et al. [6].

	Binding affinity (RRA)[a]	Oral bioavailability (%)	Systemic clearance (*L*/*h*)	Volume of distribution (*L*)
BDP MDI, 40 and 80 mcg	0.4	20	150	424
BUD DPI, 90 and 180 mcg	9.4	11	84	280
CIC MDI, 80 and 160 mcg	0.12	<1	152	897
FLU MDI, 80 mcg	1.8	20	58	96
FP MDI, 44, 110 and 220 mcg	18	≤1	66	602
FP DPI, 50, 100 and 250 mcg	18	≤1	66	602
MF DPI, 110 and 220 mcg	23	<1	53	332

BDP = beclomethasonedipropionate; BUD = budesonide; CIC = ciclesonide; FLU = flunisolide; FP = fluticasone propionate; MF = mometasonefuroate; MDI = metered dose inhaler; DPI = dry powder inhaler.

[a] Receptor binding affinities of ICSs relative to dexamethasone equal to 1; RRA: relative receptor affinity.