Fixed-Dose Combination Inhalers

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Abstract

In asthma and chronic obstructive pulmonary disease (COPD), an important step in simplifying management and improving adherence with prescribed therapy is to reduce the dose frequency to the minimum necessary to maintain disease control. Fixed-dose combination (FDC) therapy might enhance compliance by decreasing the number of medications and/or the number of daily doses. Furthermore, they have the potential for enhancing, sensitizing, and prolonging the effects of monocomponents. Combination therapy with an inhaled corticosteroid (ICS) and a long-acting β-agonist (LABA) is considered an important approach for treating patients with asthma and patients with severe COPD who have frequent exacerbations. Several ICS/LABA FDCs are now commercially available or will become available within the next few years for the treatment of COPD and/or asthma. Several studies demonstrate that there are a number of

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added benefits in using combinations of β_2-agonists and antimuscarinic agents. In particular, LABA/long-acting antimuscarinic agent (LAMA) combination seems to play an important role in optimizing bronchodilation. Several once-daily and twice-daily LABA/LAMA FDCs have been developed or are in clinical development. LAMA/ICS FDCs seem to be useful in COPD and mainly in asthma, in patients with severe asthma and persistent airflow limitation. The rationale behind the ICS/LABA/LAMA FDCs seems logical because all three agents work via different mechanisms on different targets, potentially allowing for lower doses of the individual agents to be used, accompanied by improved side effect profiles. In effect, in clinical practice, concomitant use of all three compounds is common, especially in more severe COPD but also in the treatment of adults with poorly controlled asthma despite maintenance treatment with high-dose ICS and a LABA.

Keywords

Antimuscarinic agents • Fixed-dose combinations • Inhaled corticosteroids • β2-agonists

1 Introduction

The inverse correlation between the complexity of a drug regimen and medication adherence is well established (Pan et al. 2008). Moreover, it is generally accepted that patient compliance is far better if the dosage frequency is reduced (Bjerrum et al. 2013). For diseases that require treatment with multiple drugs, safe and efficacious fixed-dose combination (FDC) therapy, that is a drug product in which two or more separate active substances are combined in a single dosage form (Bjerrum et al. 2013), offers help in addressing some of the problems of adherence (Bangalore et al. 2007). However, the benefits of combining agents are not merely additive and range from increased compliance via simple convenience to complex receptor-level synergies (Ehrick et al. 2014).

Also in asthma and chronic obstructive pulmonary disease (COPD), an important step in simplifying management and improving adherence with prescribed therapy is to reduce the dose frequency to the minimum necessary to maintain disease control (Tamura and Ohta 2007). In effect, some investigators have reported that adherence to treatment with inhalants is poor because of the complex procedures required to use them, as well as the tedious, frequent dosing (Jones et al. 2003). FDC inhalers are hypothesized to enhance compliance by decreasing the number of medications and/or the number of daily doses (Marceau et al. 2006). Furthermore, they have the potential for enhancing, sensitizing, and prolonging the effects of monocomponents (Cazzola et al. 2012a).

2 Inhaled Corticosteroid/Long-Acting β-Agonist Combinations

Inflammation plays a major role in the pathology of asthma and has an important role in COPD. ICS therapy forms the basis for treatment of asthma of all severities, improving asthma control and lung function and preventing exacerbations of disease [Global Initiative for Asthma (GINA) 2015]. Use of ICS has also been increasingly established in the treatment of COPD, particularly in symptomatic patients, who experience useful gains in quality of life (likely from an improvement in symptoms such as breathlessness and in reduction in exacerbations) and an attenuation of the yearly rate of deterioration in lung function (Cazzola et al. 2013).

The development of combinations of inhaled corticosteroids (ICSs) with long-acting β-agonists (LABAs) has led to FDC inhalers constituting the largest therapeutic segment of the respiratory market. Basically, the National Asthma Education and Prevention Program's Expert Panel Report-3 (EPR-3) (2007), the British Thoracic Society/Scottish Intercollegiate Guidelines Network (2014), and Global Initiative for Asthma (GINA) (2015) guidelines recommend using combination therapy of ICS and LABA for those patients whose asthma is not well controlled on ICS monotherapy. The use of combinations of LABAs and ICSs is also recommended for patients with COPD because, in general, the addition of LABA to ICS provides additional benefits (O'Reilly et al. 2010; Qaseem et al. 2011; Vestbo et al. 2013).

There is an exciting possibility that the observed benefit from combining these two classes of drugs might be due to a synergistic interaction, with the resulting synergetic effect being greater than the sum of responses achieved from each drug alone (Cazzola and Dahl 2004). However, the basic molecular mechanism of such an interaction is still to be fully identified although there are some mechanisms that have been documented (Barnes 2011; Chung et al. 2009). Corticosteroids increase the transcription of the β_2-adrenoceptor (β_2-AR) gene, resulting in increased expression of cell surface receptors. They may also enhance the coupling of β_2-AR to G-protein (G_s), thus enhancing β_2-agonist effects and reversing the uncoupling of β_2-AR that may occur in response to inflammatory mediators, such as IL-1β through a stimulatory effect on a G-protein-coupled receptor kinase. On the other hand, LABAs increase the translocation of glucocorticoid receptor (GR) from cytoplasm to the nucleus after activation by corticosteroids and thus enhance the anti-inflammatory effects of corticosteroids, activate CAAT/enhancer binding protein (C/EBP)α together with corticosteroids, or alter GR phosphorylation. The combination of ICSs and LABAs potentiates inhibition of CXCL8 (IL-8) and CCL11 (eotaxin) release from human airway smooth muscle cells and their proliferation and has additive effects on granulocyte-macrophage colony-stimulating factor (GM-CSF) release from epithelial cells. There are differences between LABAs that must always be considered when using an ICS/LABA combination (Cazzola et al. 2013). In fact, formoterol, but not salmeterol, reverses oxidative stress-induced corticosteroid insensitivity and decreases β_2-AR-dependent cAMP production via inhibition of PI3K-δ signaling (Rossios et al. 2012).

Moreover, it has been shown that budesonide prevents the inhibitory effects of cytokines on formoterol but not salmeterol-induced tracheal relaxation and cyclic adenosine monophosphate (cAMP) signaling (Adner et al. 2010). Formoterol increases corticosteroid sensitivity also via the activation of the serine/threonine protein phosphatase 2A (PP2A) in receptor-independent manner (Kobayashi et al. 2012).

ICS/LABA FDC therapy is the preferred treatment for the long-term treatment of persistent asthma when a medium dose of ICS alone fails to achieve control of asthma [National Asthma Education and Prevention Program's Expert Panel Report-3 (EPR-3) 2007; British Thoracic Society/Scottish Intercollegiate Guidelines Network 2014; Global Initiative for Asthma (GINA) 2015]. Systematic reviews have shown that adding a LABA to low-dose ICS in poorly controlled asthma patients is more effective in reducing the risk of asthma exacerbations than using higher doses of ICS (Ducharme et al. 2010). The protective effect of ICS/LABA combination therapy appeared particularly effective in the following clinically relevant subgroups: individuals 18 years or older, males, African American individuals, and individuals with either moderate-to-severe or severe asthma at baseline (Wells et al. 2012). Obviously, a combination inhaler must always be used, because in many patients, the use of separate inhalers will inevitably result in periods of LABA monotherapy because of poor compliance with ICSs in standard clinical practice. In any case, ICS/LABA combination therapy results in a more rapid improvement in asthma symptoms, lung function, and airway inflammation compared to ICS monotherapy in steroid-naive patients with asthma (Matsunaga et al. 2013). Moreover, there are cost savings when using the combined products compared to the use of individual LABA and ICS inhalers (Shepherd et al. 2008).

Unfortunately, there is still a lack of knowledge regarding safety of LABAs with concomitant ICSs use, with both theoretical arguments and limited empirical evidence that ICSs may mitigate LABA-associated risks (Beasley et al. 2010). However, the current evidence from non-randomized studies shows that combined treatment of LABAs and ICSs is not associated with higher risk of serious adverse events (Hernández et al. 2014).

Nonetheless, since there are no studies showing that LABAs (alone or in conjunction with ICSs) increase survival or positively affect severe asthma exacerbations (those necessitating intubation or hospital-based care), and their serious risks, the FDA recommended that use of the LABA must be stopped, if possible, once asthma control is achieved and the use of an asthma-controller medication, such as an ICS, then be maintained (Chowdhury and Dal Pan 2010). LABAs should be reserved only for patients whose asthma cannot be adequately managed with asthma-controller medication such as an ICS (Chowdhury and Dal Pan 2010).

In COPD, therapy with ICS/LABA is associated with slower progression of lung function loss, decreased exacerbation rate, and improved health-related quality of life compared with treatment with LABAs alone, at least in a subset of patients with a favorable response to treatment with ICSs (Cazzola et al. 2013). Combination therapy is associated with significant difference in mortality when compared to

placebo alone but not with LABA alone (Nannini et al. 2012). Intriguingly, ICSs in combination with LABAs might also reduce cardiovascular disease and all-cause mortality (Zervas et al. 2013). Withdrawal from treatment with ICS on patients with ICS/LABA combination therapy may lead to exacerbation of COPD in some patients (van der Valk et al. 2002). Nonetheless, the risk of pneumonia with ICS/LABA is increased compared with either LABA or placebo and is dose dependent (Crim et al. 2009). In the Investigating New Standards for Prophylaxis in Reduction of Exacerbations (INSPIRE) study, the excess of pneumonia events in patients treated with an ICS/LABA combination treatment was mainly caused by exacerbations that failed to resolve (Calverley et al. 2011). Patients at greater risk of pneumonia with ICS/LABA have more severe obstruction and either a body mass index <19 kg/m^2 or a pneumonia history and comorbidities (DiSantostefano et al. 2014). Multiple comorbidities and use of psychoanaleptics also contribute to an increased risk of pneumonia in more obstructed patients. Patients treated with ICS have a higher airway bacterial load (Garcha et al. 2012), although whether this is a causal association and relates to the greater number of pneumonia events remains to be determined.

The benefits and, but even more, drawbacks of ICSs in COPD explain why all national and international COPD guidelines recommend ICS/LABA FDCs only for patients with severe impairment and high risk of exacerbations (O'Reilly et al. 2010; Qaseem et al. 2011; Vestbo et al. 2013). Actually, ICSs are recommended in combination with LABAs for those patients who have few symptoms but are at a high risk of exacerbations, for those patients who have many symptoms and a high risk of exacerbations [Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015], and also for those suffering from for the asthma–COPD overlap syndrome (Miravitlles et al. 2014).

Several ICS/LABA FDCs (fluticasone propionate/salmeterol, budesonide/formoterol, beclomethasone/formoterol, fluticasone propionate/formoterol, mometasone/formoterol, fluticasone furoate/vilanterol, mometasone/indacaterol, ciclesonide/formoterol) are now commercially available or will become available within the next few years for the treatment of COPD and/or asthma.

Despite sharing a similar basic mechanism of action, ICSs differ in terms of pharmacokinetic characteristics, and this may determine important difference in their efficacy and safety as a result of the different chemical structures of individual agents. This is the case also for LABAs. Unfortunately, there are insufficient clinical data to determine whether there are clinically important differences in efficacy between the various ICS/LABA FDCs. 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 (Papi et al. 2014). Important properties for a LABA include speed of onset of action, duration of action, and agonist activity at the β_2-adrenoceptor (Papi et al. 2014).

The PATHOS study (An Investigation of the Past 10 Years Health Care for Primary Care Patients with Chronic Obstructive Pulmonary Disease), a population-based, retrospective, observational registry study conducted in Sweden, found that

long-term budesonide/formoterol treatment was associated with fewer moderate and severe COPD exacerbations than long-term treatment with fluticasone propionate/salmeterol (Larsson et al. 2013). The findings were robust irrespective of the exacerbation definition used and were not affected by several sensitivity analyses. Compared with budesonide/formoterol, rates of pneumonia, admission to hospital, and mortality related to pneumonia were higher in patients treated with fluticasone propionate/salmeterol (Janson et al. 2013). It has been suggested that since the immunosuppressant potency of fluticasone is reported to be up to tenfold higher than that of budesonide with regard to ex vivo inhibition of human alveolar macrophage innate immune response to bacterial triggers (Ek et al. 1999), this factor alone could explain these findings (Janson et al. 2013). Also differences in pharmacokinetic and pharmacodynamic properties related to differences in lipophilicity and hydrophilicity profiles between fluticasone propionate and budesonide might explain the greater risk of pneumonia with fluticasone. The highly lipophilic fluticasone molecule can remain in the mucosa and epithelial lining fluid of the bronchi longer than budesonide (Dalby et al. 2009), inducing a more potent and longer suppression of local immunity than budesonide, thereby causing an increased risk of local bacterial proliferation and a pneumonia outbreak in patients with severe COPD (Janson et al. 2013).

3 Long-Acting Anti-muscarinic Agent/Long-Acting β-Agonist Combinations

Targeting one bronchodilatory pathway alone may not 'optimize' bronchodilation because airway smooth muscle tone is influenced by more than one nerve system (Cazzola et al. 2012a). Therefore it is not surprising that reversibility (defined as $\geq$15 % increase in post-bronchodilator FEV_1) can be shown with combination salbutamol plus ipratropium in up to two-thirds of COPD patients (Tashkin et al. 2008).

The combination of two bronchodilators with different mechanisms of action to treat patients with COPD is an established medical practice (COMBIVENT Inhalation Aerosol Study Group 1994) and, in any case, several trials have documented that the free combination of a long-acting antimuscarinic agent (LAMA) and a LABA provides significant and sustained improvement in bronchodilation versus alone from day 1, with significant improvements in patient-centered outcomes (Mahler et al. 2012; Vincken et al. 2014; ZuWallack et al. 2014).

The pharmacological mechanism that justifies the combinations of bronchodilators is complex and lies also in the reciprocal influences of cholinergic and adrenergic systems at presynaptic and postsynaptic level (Belmonte 2005; Cazzola and Molimard 2010; Meurs et al. 2013; Pera and Penn 2014). It includes the activation of β_2-ARs and the block of M_3 muscarinic receptors at postsynaptic level. At postsynaptic level β_2-AR signaling limits M_3 mAChR-mediated inositol triphosphate (IP_3) production by several distinct mechanisms, most presumed to involve protein kinase A (PKA). In the other side, the M_3 mAChR blockade seems

to have a great influence on the relaxation induced by β-agonists, presumably blocking the resulting activation of protein kinase C (PKC) and the subsequent phosphorylation of β2-AR and/or G_s protein. Anti-muscarinic agents, inhibiting the postsynaptic G_i-coupled M_2 muscarinic receptors, maintain the ASM relaxation induced by β_2-agonists and sustain adenylyl cyclase (AC) activity. The inhibition of presynaptic M_2 muscarinic receptor may increase the release of acetylcholine into the synaptic space. At presynaptic level, β_2-agonists can decrease the release of acetylcholine (ACh) via a modulation of cholinergic neurotransmission that involves calcium-activated potassium (K_{Ca}) channels. Activation of K_{Ca} channels is thought to hyperpolarize the cell membrane, thus causing reductions in the concentration of intracellular Ca^{2+} and ACh release in prejunctional cholinergic nerves. By contrast, activation of AC enhances ACh release.

Some data seem to indicate that LABA/LAMA combination is able to elicit synergistic effects on isolated human bronchi (Cazzola et al. 2014). A modest synergistic effect in vivo, in patients with COPD, has also been demonstrated (Cazzola et al. 2015a).

The dissimilarities in the onset and duration of action of LABA and LAMA and, in any case, the differences in the devices used for the delivery of these drugs make free combinations uncomfortable and therefore unpredictable, especially if focused on adherence to prescribed treatment (Matera et al. 2015a). It is therefore obvious that there is the need for FDCs of bronchodilators in a single inhaler.

Since it is hoped that FDCs could offer advantages of better compliance, adherence, and cost-efficacy in addition to synergistic action of the components in free combinations in separate devices, several once-daily LABA/LAMA combinations, including QVA149 (combination of indacaterol and glycopyrronium bromide), vilanterol plus umeclidinium bromide, and olodaterol plus tiotropium bromide, have been developed or are in clinical development as FDCs (Cazzola and Matera 2014a).

The results of the pivotal Phase III IGNITE and EXPEDITION programs show that indacaterol/glycopyrronium (QVA149) is able to elicit a significant improvement in lung function and patient-reported outcomes, including breathlessness and rescue medication use, reduced rates of COPD exacerbations, and HRQoL when compared with current standard of care. Moreover, QVA149 is generally well tolerated, with most adverse events being of mild-to-moderate severity (Matera et al. 2015a). Several pivotal clinical trials have documented that also vilanterol/umeclidinium bromide (Matera et al. 2015b) and olodaterol/tiotropium bromide (Buhl et al. 2015) FDCs impact favorably on lung function and other outcome measures such as quality of life, dyspnea, rescue medication use, and exercise capacity, with no clinically meaningful treatment-related changes in vital signs or clinical laboratory parameters.

As there is a progressive attempt to shift attention toward controlling nocturnal symptoms and those present on awakening, which are indicated by epidemiologic studies to be the most troublesome for COPD patients (Kessler et al. 2011), the twice-daily dosing of bronchodilators is still considered a useful approach at least for the symptomatic treatment of COPD. Therefore, two twice-daily LABA/LAMA

FDCs, formoterol/aclidinium bromide and formoterol/glycopyrronium bromide, are under development. Formoterol/aclidinium bromide FDC has been evaluated in COPD patients and evidence suggests that it is efficacious and safe, has a quick onset of action, and is well tolerated (Cazzola et al. 2015b). Formoterol/glycopyrronium bromide (PT003), which is delivered via the eFlow Nebulizer System, is in an earlier stage of development.

4 Inhaled Corticosteroid/Long-Acting Antimuscarinic Agent Combinations

Very few studies published to date have been designed specifically to evaluate the effect of LAMA/ICS combinations on clinical outcomes, and this is an area that warrants future study. Nevertheless, there is evidence that COPD patients demonstrate not only superior spirometric responses but also improved clinically important end points such as dyspnea, health status, and frequency of exacerbations with a LAMA plus an ICS compared with a LABA plus an ICS (Hodder et al. 2007). No LAMA has received regulatory approval for asthma treatment, but there is a growing body of evidence to support the efficacy the addition of tiotropium to an ICS in patients with severe asthma and persistent airflow limitation, with reported improvements in symptoms and/or lung function, an extended time to first asthma exacerbation, and a reduced risk of severe exacerbations (Beeh et al. 2014; Kerstjens et al. 2012; Peters et al. 2010), leading to inclusion of these data in current asthma guidelines [Global Initiative for Asthma (GINA) 2015].

Experimental evidence suggests an influence of corticosteroids on muscarinic receptors. It has been shown that treatment of rats with dexamethasone for 1 week resulted in decreased acetylcholine concentration in the surface epithelium of trachea and intestine, which was accompanied by a reduction in choline acetyltransferase activity (Reinheimer et al. 1998). Moreover, at least in dogs, a treatment with methylprednisolone led to a decreased expression of both M_2 and M_3 muscarinic receptors in airway smooth muscle (Emala et al. 1997) by attenuation of a factor-controlling receptor gene expression. It has also been documented that dexamethasone decreases airway responsiveness to vagus nerve stimulation via two mechanisms: increased M_2 receptor function that results in decreased acetylcholine release and increased degradation of acetylcholine by cholinesterases (Jacoby et al. 2001). It has also been reported that dexamethasone protects against virally induced or antigen-induced M_2-receptor dysfunction and associated hyperresponsiveness (Moreno et al. 2003). Interestingly, glycopyrronium acts synergistically with budesonide in inhibiting inflammatory mediators (Pahl et al. 2006).

Fluticasone furoate/umeclidinium bromide FDC is under development. An initial study demonstrated convincing evidence of a bronchodilating effect of umeclidinium in patients with asthma uncontrolled on ICS and further showed that the effect was greater in patients with fixed versus non-fixed obstruction (Lee et al. 2015).

A phase I study that aimed to compare the systemic exposure to tiotropium and CD 1857 after treatment with the FDC of tiotropium plus BI 54903, a nonsteroidal selective glucocorticoid receptor agonist, when administered once-daily over 21 days via Respimat in healthy volunteers, has been completed. However, results have not been disclosed yet (Cazzola et al. 2012b).

5 Inhaled Corticosteroid/Long-Acting β-Agonist/ Long-Acting Antimuscarinic Agent Combinations

The growing body of evidence suggests that triple therapy with ICS, LABAs, and LAMAs is efficacious, making it an attractive combination in COPD (Cazzola and Matera 2014b). For patients who remain symptomatic despite LABA-ICS combination, GOLD recommends triple therapy with LAMA, LABA, and ICS [Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015]. The rationale behind this seems logical because all three agents work via different mechanisms on different targets, potentially allowing for lower doses of the individual agents to be used, accompanied by improved side effect profiles. In effect, in clinical practice concomitant use of all three compounds is common, especially in more severe COPD (Ross and Hansel 2014).

Similarly, an add-on LAMA is effective and well tolerated in the treatment of adults with poorly controlled asthma despite maintenance treatment with high-dose ICS and a LABA (McKeage 2015). Thus, LAMAs can provide a valuable option in this difficult-to-treat patient group. Accordingly, a variety of triple combinations are currently under development (Cazzola and Matera 2014b). These inhalers may well improve compliance, but titration of individual component drug doses may prove difficult, and disease severity seems to affect the drug dose–response curve (Ross and Hansel 2014).

Triohale pressurized Metered-Dose Inhaler (pMDI) has been marketed as the world's first triple-combination inhaler to be taken only once a day (ciclesonide 200 μg, formoterol fumarate 6 μg, tiotropium 9 μg,) and is already available in India. This formulation is a suspension-based product and is the only pMDI to contain three therapeutics in one device.

Budesonide, formoterol fumarate, and glycopyrronium pMDI (PT010), a ICS/LAMA/LABA FDC in Pearl Therapeutics' cosuspension technology, the FDC beclomethasone/formoterol plus glycopyrronium (CHF5993) taken twice daily, and fluticasone furoate/vilanterol/umeclidinium are developed once on a daily basis are under clinical evaluation. It is likely that also a FDC with mometasone + indacaterol + glycopyrronium will be developed on a once-daily basis. However, to date there is still no information available regarding it.

References

Adner M, Larsson B, Säfholm J, Naya I, Miller-Larsson A (2010) Budesonide prevents cytokine-induced decrease of the relaxant responses to formoterol and terbutaline, but not to salmeterol, in mouse trachea. J Pharmacol Exp Ther 333:273–280

Bangalore S, Kamalakkannan G, Parkar S, Messerli FH (2007) Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med 120:713–719

Barnes PJ (2011) Glucocorticosteroids: current and future directions. Br J Pharmacol 163:29–43

Beasley R, Perrin K, Weatherall M, Wijesinghe M (2010) Call for withdrawal of LABA single-therapy inhaler in asthma. Lancet 376:750–751

Beeh KM, Moroni-Zentgraf P, Ablinger O, Hollaenderova Z, Unseld A, Engel M et al (2014) Tiotropium Respimat® in asthma: a double-blind, randomised, dose-ranging study in adult patients with moderate asthma. Respir Res 15:61

Belmonte KE (2005) Cholinergic pathways in the lungs and anticholinergic therapy for chronic obstructive pulmonary disease. Proc Am Thorac Soc 2:297–304

Bjerrum OJ, Gautam Y, Bjerrum EJ, Schmiegelow M, Boonen HC (2013) Medicines combinations options and regulatory hurdles. Eur J Pharm Sci 49:659–663

British Thoracic Society/Scottish Intercollegiate Guidelines Network (2014) British guideline on the management of asthma. Thorax 69 Suppl 1:1–192

Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G et al (2015) Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2–4). Eur Respir J 45:969–979

Calverley PM, Stockley RA, Seemungal TA, Hagan G, Willits LR, Riley JH et al (2011) Reported pneumonia in patients with COPD: findings from the INSPIRE study. Chest 139:505–512

Cazzola M, Dahl R (2004) Inhaled combination therapy with long-acting β_2-agonists and corticosteroids in stable COPD. Chest 126:220–237

Cazzola M, Matera MG (2014a) Bronchodilators: current and future. Clin Chest Med 35:191–201

Cazzola M, Matera MG (2014b) Triple combinations in chronic obstructive pulmonary disease - is three better than two? Expert Opin Pharmacother 15:2475–2478

Cazzola M, Molimard M (2010) The scientific rationale for combining long-acting β_2-agonists and muscarinic antagonists in COPD. Pulm Pharmacol Ther 23:257–267

Cazzola M, Page CP, Calzetta L, Matera MG (2012a) Pharmacology and therapeutics of bronchodilators. Pharmacol Rev 64:450–504

Cazzola M, Rogliani P, Segreti A, Matera MG (2012b) An update on bronchodilators in Phase I and II clinical trials. Expert Opin Investig Drugs 21:1489–1501

Cazzola M, Rogliani P, Novelli L, Matera MG (2013) Inhaled corticosteroids for chronic obstructive pulmonary disease. Expert Opin Pharmacother 14:2489–2499

Cazzola M, Calzetta L, Page CP, Rogliani P, Facciolo F, Gavaldà A et al (2014) Pharmacological characterization of the interaction between aclidinium bromide and formoterol fumarate on human isolated bronchi. Eur J Pharmacol 745:135–143

Cazzola M, Calzetta L, Segreti A, Facciolo F, Rogliani P, Matera MG (2015a) Translational study searching for synergy between glycopyrronium and indacaterol. COPD 12:175–181

Cazzola M, Calzetta L, Matera MG (2015b) Aclidinium/formoterol fixed-dose combination for the treatment of chronic obstructive pulmonary disease. Drugs Today (Barc) 51:97–105

Chowdhury BA, Dal Pan G (2010) The FDA and safe use of long-acting beta-agonists in the treatment of asthma. N Engl J Med 362:1169–1171

Chung KF, Caramori G, Adcock IM (2009) Inhaled corticosteroids as combination therapy with β-adrenergic agonists in airways disease: present and future. Eur J Clin Pharmacol 65:853–871

COMBIVENT Inhalation Aerosol Study Group (1994) In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. Chest 105:1411–1419

Crim C, Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C et al (2009) Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. Eur Respir J 34:641–647

Dalby C, Polanowski T, Larsson T, Borgstrom L, Edsbacker S, Harrison TW (2009) The bioavailability and airway clearance of the steroid component of budesonide/formoterol and salmeterol/fluticasone after inhaled administration in patients with COPD and healthy subjects: a randomized controlled trial. Respir Res 10:104

DiSantostefano RL, Li H, Hinds D, Galkin DV, Rubin DB (2014) Risk of pneumonia with inhaled corticosteroid/long-acting β2 agonist therapy in chronic obstructive pulmonary disease: a cluster analysis. Int J Chron Obstruct Pulmon Dis 9:457–468

Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ (2010) Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. Cochrane Database Syst Rev 4, CD00553

Ehrick JD, Wylie J, Goodey AP, Li Y, Liu O, Donovan B (2014) Orally inhaled fixed-dose combination products for the treatment of asthma and chronic obstructive pulmonary disease: not simple math. Ther Deliv 5:297–317

Ek A, Larsson K, Siljerud S, Palmberg L (1999) Fluticasone and budesonide inhibit cytokine release in human lung epithelial cells and alveolar macrophages. Allergy 54:691–699

Emala CW, Clancy J, Hirshman CA (1997) Glucocorticoid treatment decreases muscarinic receptor expression in canine airway smooth muscle. Am J Physiol 272:L745–L751

Garcha DS, Thurston SJ, Patel AR, Mackay AJ, Goldring JJ, Donaldson GC et al (2012) Changes in prevalence and load of airway bacteria using quantitative PCR in stable and exacerbated COPD. Thorax 67:1075–1080

Global Initiative for Asthma (GINA) (2015) Global Strategy for Asthma Management and Prevention. Available from: http://www.ginasthma.org/local/uploads/files/GINA_Report_2015.pdf

Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2015) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf

Hernández G, Avila M, Pont A, Garin O, Alonso J, Laforest L et al (2014) Long-acting beta-agonists plus inhaled corticosteroids safety: a systematic review and meta-analysis of non-randomized studies. Respir Res 15:83

Hodder R, Kesten S, Menjoge S, Viel K (2007) Outcomes in COPD patients receiving tiotropium or salmeterol plus treatment with inhaled corticosteroids. Int J Chron Obstruct Pulmon Dis 2:157–167

Jacoby DB, Yost BL, Kumaravel B, Chan-Li Y, Xiao HQ, Kawashima K et al (2001) Glucocorticoid treatment increases inhibitory m_2 muscarinic receptor expression and function in the airways. Am J Respir Cell Mol Biol 24:485–91

Janson C, Larsson K, Lisspers KH, Ställberg B, Stratelis G, Goike H et al (2013) Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting β_2 agonist: observational matched cohort study (PATHOS). BMJ 346:f3306

Jones C, Santanello NC, Boccuzzi SJ, Wogen J, Strub P, Nelsen LM (2003) Adherence to prescribed treatment for asthma: evidence from pharmacy benefits data. J Asthma 40:93–101

Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M et al (2012) Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med 367:1198–1207

Kessler R, Partridge MR, Miravitlles M, Cazzola M, Vogelmeier C, Leynaud D et al (2011) Symptom variability in patients with severe COPD: a pan-European cross-sectional study. Eur Respir J 37:264–272

Kobayashi Y, Mercado N, Miller-Larsson A, Barnes PJ, Ito K (2012) Increased corticosteroid sensitivity by a long acting β_2 agonist formoterol via β_2 adrenoceptor independent protein phosphatase 2A activation. Pulm Pharmacol Ther 25:201–207

Larsson K, Janson C, Lisspers K, Jørgensen L, Stratelis G, Telg G et al (2013) Combination of budesonide/formoterol more effective than fluticasone/salmeterol in preventing exacerbations in chronic obstructive pulmonary disease: the PATHOS study. J Intern Med 273:584–594

Lee LA, Yang S, Kerwin E, Trivedi R, Edwards LD, Pascoe S (2015) The effect of fluticasone furoate/umeclidinium in adult patients with asthma: a randomized, dose-ranging study. Respir Med 109:54–62

Mahler DA, D'Urzo A, Bateman ED, Ozkan SA, White T, Peckitt C et al (2012) Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison. Thorax 67:781–788

Marceau C, Lemière C, Berbiche D, Perreault S, Blais L (2006) Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. J Allergy Clin Immunol 118:574–581

Matera MG, Rogliani P, Cazzola M (2015a) QVA149 (indacaterol/glycopyrronium) for the treatment of chronic obstructive pulmonary disease. Expert Opin Pharmacother 16:1079–1090

Matera MG, Rogliani P, Rinaldi B, Cazzola M (2015b) Umeclidinium bromide + vilanterol for the treatment of chronic obstructive pulmonary disease. Expert Rev Clin Pharmacol 8:35–41

Matsunaga K, Kawabata H, Hirano T, Sugiura H, Minakata Y, Ichinose M (2013) Difference in time-course of improvement in asthma control measures between budesonide and budesonide/formoterol. Pulm Pharmacol Ther 26:189–194

McKeage K (2015) Tiotropium Respimat®: a review of its use in asthma poorly controlled with inhaled corticosteroids and long-acting β_2-adrenergic agonists. Drugs 75:809–816

Meurs H, Dekkers BG, Maarsingh H, Halayko AJ, Zaagsma J, Gosens R (2013) Muscarinic receptors on airway mesenchymal cells: novel findings for an ancient target. Pulm Pharmacol Ther 26:145–155

Miravitlles M, Soler-Cataluña JJ, Calle M, Molina J, Almagro P, Quintano JA et al (2014) Spanish guideline for COPD (GesEPOC). Update 2014. Arch Bronconeumol 50 Suppl 1:1–16

Moreno L, Jacoby DB, Fryer AD (2003) Dexamethasone prevents virus-induced hyperresponsiveness via multiple mechanisms. Am J Physiol Lung Cell Mol Physiol 285: L451–L455

Nannini LJ, Lasserson TJ, Poole P (2012) Combined corticosteroid and long-acting beta$_2$-agonist in one inhaler versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 9, CD006829

O'Reilly J, Jones MM, Parnham J, Lovibond K, Rudolf M (2010) Management of stable chronic obstructive pulmonary disease in primary and secondary care: summary of updated NICE guidance. BMJ 340:c3134

Pahl A, Bauhofer A, Petzold U, Cnota PJ, Maus J, Brune K et al (2006) Synergistic effects of the anti-cholinergic R, R-glycopyrrolate with anti-inflammatory drugs. Biochem Pharmacol 72:1690–1696

Pan F, Chernew ME, Fendrick AM (2008) Impact of fixed-dose combination drugs on adherence to prescription medications. J Gen Intern Med 23:611–614

Papi A, Blasi F, Canonica GW, Cazzola M, Centanni S, Foschino Barbaro MP et al (2014) Fluticasone propionate/formoterol: a fixed-combination therapy with flexible dosage. Eur J Intern Med 25:695–700

Pera T, Penn RB (2014) Crosstalk between beta-2-adrenoceptor and muscarinic acetylcholine receptors in the airway. Curr Opin Pharmacol 16:72–81

Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT et al (2010) Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med 363:1715–1726

National Asthma Education and Prevention Program (2007) Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma–summary report 2007. J Allergy Clin Immunol 120(5 Suppl):S94–S138

Qaseem A, Wilt TJ, Weinberger SE, Hanania NA, Criner G, van der Molen T et al (2011) Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest

Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med 155:179–191

Reinheimer T, Münch M, Bittinger F, Racké K, Kirkpatrick CJ, Wessler I (1998) Glucocorticoids mediate reduction of epithelial acetylcholine content in the airways of rats and humans. Eur J Pharmacol 349:277–284

Ross CL, Hansel TT (2014) New drug therapies for COPD. Clin Chest Med 35:219–239

Rossios C, To Y, Osoata G, Ito M, Barnes PJ, Ito K (2012) Corticosteroid insensitivity is reversed by formoterol via phosphoinositide-3-kinase inhibition. Br J Pharmacol 167:775–786

Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D et al (2008) Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over. Health Technol Assess 12(19):iii–iv. 1–360

Tamura G, Ohta K (2007) Adherence to treatment by patients with asthma or COPD: comparison between inhaled drugs and transdermal patch. Respir Med 101:1895–1902

Tashkin DP, Celli B, Decramer M, Liu D, Burkhart D, Cassino C et al (2008) Bronchodilator responsiveness in patients with COPD. Eur Respir J 31:742–750

van der Valk P, Monninkhof E, van der Palen J, Zielhuis G, van Herwaarden C (2002) Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. Am J Respir Crit Care Med 166:1358–1363

Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A et al (2013) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 187:347–365

Vincken W, Aumann J, Chen H, Henley M, McBryan D, Goyal P (2014) Efficacy and safety of coadministration of once-daily indacaterol and glycopyrronium versus indacaterol alone in COPD patients: the GLOW6 study. Int J Chron Obstruct Pulmon Dis 9:215–228

Wells KE, Peterson EL, Ahmedani BK, Severson RK, Gleason-Comstock J, Williams LK (2012) The relationship between combination inhaled corticosteroid and long-acting β-agonist use and severe asthma exacerbations in a diverse population. J Allergy Clin Immunol 129:1274–1279

Zervas E, Samitas K, Gaga M, Beghe B, Fabbri LM (2013) Inhaled corticosteroids in COPD: pros and cons. Curr Drug Targets 14:192–224

ZuWallack R, Allen L, Hernandez G, Ting N, Abrahams R (2014) Efficacy and safety of combining olodaterol Respimat® and tiotropium HandiHaler® in patients with COPD: results of two randomized, double-blind, active-controlled studies. Int J Chron Obstruct Pulmon Dis 9:1133–1144