The MABA approach: a new option to improve bronchodilator therapy

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MABA agents provide a new approach to dual bronchodilator therapy by combining muscarinic antagonism and beta 2-agonism http://ow.ly/mXXdZ

Recently, the results of an interesting systematic review have shown that the use of a combination of a long-acting β_2-agonist (LABA) and a long-acting antimuscarinic agent (LAMA), the so called ''dual'' bronchodilator therapy, in stable moderate chronic obstructive pulmonary disease (COPD) patients is potentially a good pharmacological approach for the improvement of symptoms when they are not adequately controlled with tiotropium monotherapy [1]. Several studies have demonstrated a superior bronchodilation effect of combining a LABA with a LAMA compared with the individual agents alone, and that these combinations are well tolerated in patients with moderate to severe COPD [2]. Published evidence also indicates that ''dual'' bronchodilator therapies induce greater improvements in patient-centred outcomes such as dyspnoea, symptoms, rescue medication use and health-related quality of life than individual drugs used alone [3].

These findings are not surprising because the pharmacological rationale that supports this therapeutic possibility seems to be solid [4]. LABAs and LAMAs directly target airway smooth muscle working through different pathways [4, 5]. Moreover, several intriguing preclinical data support cross-activity of acetylcholine on the sympathetic system and adrenergic catecholamines on the parasympathetic (acetylcholine neurotransmission) system [4–6].

All this explains why the new executive summary of the Global Initiative for Chronic Obstructive Lung Disease recommends a combination of long-acting bronchodilators as a second choice in COPD patients who have significant symptoms but still a low risk of exacerbations, or have few symptoms but a high risk of exacerbations [7]. A combination of long-acting bronchodilators is a second choice also in patients who have many symptoms and a high risk of exacerbations, but it must be associated with an inhaled corticosteroid [7].

Nonetheless, there is still no unanimous agreement about whether and when a second bronchodilator with a different mechanism of action can be added in patients with stable COPD [8]. Even the updated COPD guidelines recently released by the American College of Physicians, the American College of Chest Physicians, the American Thoracic Society and the European Respiratory Society [9] do not offer any guidance on when to use ''dual'' bronchodilator therapy or triple therapy, with an additional inhaled corticosteroid.

Another important problem that we should always consider when we need to prescribe two or more drugs simultaneously to a patient with COPD is represented by the fact that the prescribed number of drugs and

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doses per day are inversely related to adherence [10]. Non-adherence to medication plans is a major obstacle to successful management of chronic obstructive airway diseases [11]. In general, adherence to inhaled drugs is a multifactorial outcome in which tedious frequent dosing and the use of multiple inhalers play a crucial role [12]. For this reason, it has been suggested that drugs are prescribed in a fixed combination and/or a low dosing frequency for the medication-based management of COPD, in order to enhance adherence in routine clinical practice [5, 10].

Bi-functional (or dual pharmacophore) muscarinic β_2-agonist (MABA) agents are a novel approach to ''dual'' bronchodilator therapy by combining muscarinic antagonism and β_2-agonism in a single molecule [13].

This approach may offer several advantages over combination therapy of two separate drug entities [5]. They include the benefit of delivering a fixed ratio into every region of the lung reducing the complexity of combination inhalers, a single pharmacokinetic profile, a uniform ratio of activities at the cellular level, and a simplified clinical development programme. However, one limitation of MABA molecules is that the ratio of muscarinic antagonism and β_2-agonism activities cannot be adjusted as needed and this limits dosing flexibility [13].

The complementary nature of the muscarinic acetylcholine receptor bronchoconstriction and β_2-adrenoceptor bronchodilation pathways has attracted considerable effort in the discovery of dual pharmacology MABA compounds [13]. The reasons for companies to develop a MABA product are numerous. MABAs offer an enhanced patent position and this is a crucial point for their commercial strategies. Another key advantage for companies consists in the fact that a single molecule that confers both therapeutic effects can avoid the approval of each component separately as well as in combination and may be a faster and less expensive route to regulatory approval [14]. Since MABAs offer benefits in terms of ease-of-use, it seems logical to expect that convenience and consequently compliance, which means adherence to the prescribed treatment, would probably be improved. Moreover, patients cannot take one agent without taking the other.

The MABA approach circumvents the potential problem of formulating different drugs in one inhaler, providing a fixed ratio of muscarinic antagonism and β_2-agonism with simplified formulation and pharmacokinetics compared with combination therapy [15]. Moreover, it may also offer a unique opportunity, if united with an anti-inflammatory agent (*e.g.* an inhaled corticosteroid), for the simplification of the somewhat more technically challenging triple combination approach to therapy. In fact, as correctly highlighted by NORMAN [16], formulating an aerosol product comprising three active ingredients is seen as too problematic but the availability of a MABA provides the opportunity to develop combinations that combine corticosteroids with two bronchodilator activities and, thus, potentially achieve better efficacy than is seen with the current combination products dominating the treatment of asthma and COPD. This is a very important concept because for patients with more severe COPD, such as those with frequent exacerbations, a logical next step in the treatment pathway is triple therapy with a LABA, LAMA and an inhaled corticosteroid [7].

GSK961081 (formerly TD5959) developed by GlaxoSmithKline and Theravance, Inc. will likely be the first MABA to be commercialised. In this issue of *European Respiratory Journal*, WIELDERS *et al.* [17] present data from a phase IIb 4-week dose-finding trial. GSK961081 was able to elicit a bronchodilator effect that was significantly greater than that induced by salmeterol in moderate and severe COPD patients, with 400 μg per day the best dosage. Moreover, it appeared safe and well tolerated. However, the results of this study do not allow us to establish whether it is preferable to administer the drug once a day or twice a day. Nonetheless, a 2-week trial in which GSK961081 400 μg once a day was compared with tiotropium 18 μg once a day plus salmeterol 50 μg twice a day, has shown that GSK961081 was able to induce sustained bronchodilation similar to tiotropium plus salmeterol, but with a more rapid onset of action [18].

We do not do not know if 400 μg per day will be the dose actually used in the further development of the drug. NORRIS and AMBERY [19] have recently shown that the maximal increase in forced expiratory volume in 1 s after single doses of GSK961081 400 μg or 1200 μg plus cumulative doses of salbutamol or ipratropium was greater than that observed with GSK961081 doses plus placebo. This finding suggests that, even at a dose of 1200 μg, GSK961081 is not able to induce a maximal bronchodilation. However, this last trial [19] and a previous study [18] showed that once daily 400 μg and 1200 μg have comparable efficacy. In any case, the documentation that the residual bronchodilation following salbutamol and ipratropium inhalation was similar [19] seems to be more important. In fact, this indirect assessment may indicate that the activities of the muscarinic antagonism and β_2-agonism components are of a similar magnitude.

All the above features make us believe that GSK961081 may represent a real advance in bronchodilator therapy because it seems to have the potential to simplify therapy and ensure, thereby, adherence to it.

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However, we are still lacking important information. In particular, a long-term comparison with a once a day LABA/LAMA fixed dose combination is mandatory. Moreover, given the presence of both the muscarinic antagonism and β_2-agonism components, a thorough long-term assessment of cardiac safety is unquestionably necessary. Of course, this assessment should not leave aside the device that will be used to deliver the drug.

A final crucial point that could be raised by regulatory authorities is represented by what might happen when a patient on a regular MABA, suddenly suspend such treatment. The combination of muscarinic antagonism and β_2-agonism activities might theoretically cause a downregulation of β_2-adrenoceptors and an upregulation of muscarinic acetylcholine receptors. β-Adrenoceptor function and regulation are altered by chronic β-agonist activation [5]. In fact, repetitive β_2-agonist use may lead not only to reduced bronchoprotection but also to sensitisation of excitation–contraction signalling pathways. The observation that recurrent β_2-adrenoceptor activation leads to functional receptor desensitisation is not surprising since receptor desensitisation is a normal homeostatic process that presumably serves to protect cells from excessive stimulation [20]. Nonetheless, the efficacy of short-acting β_2-agonists can be significantly attenuated during regular use of LABAs and this indicates relevant tolerance to rescue β_2-agonist treatment [21]. Conversely, regular exposure to antimuscarinic drugs would be expected to upregulate airway muscarinic receptors and could cause a transient increase in airways obstruction if treatment is stopped or omitted [22]. Thus, there should be a concern that MABAs might increase the risk of less reversibility if a COPD patient would suffer an ''acute'' bronchoconstriction. However, we believe that this is just a hypothetical concern because there is no data in the literature that confirms the occurrence of this phenomenon when patients are regularly treated with a LABA/LAMA combination and stop or omit it.

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