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COMMENTARY

Optimizing the Development Strategy of Combination Therapy in Respiratory Medicine: From Isolated Airways to Patients

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ABSTRACT

The current recommendations for the treatment of chronic obstructive pulmonary disease (COPD) are pushing towards triple combination therapy based on the combination of an inhaled corticosteroid (ICS) associated with two bronchodilator agents. However, dual bronchodilation remains the cornerstone for the treatment of most COPD patients. Combining a long-acting β_2 adrenoceptor agonist (LABA) with a long-acting muscarinic antagonist (LAMA) induces appreciable synergistic bronchorelaxant effect in human airways, especially when the medications are combined at isoeffective concentrations. Thus, each LABA/LAMA combination is characterized by a specific range of concentration-ratio at which the drug mixture may induce sustained synergistic interaction. Results of a recent randomized controlled trial (RCT, NCT00696020) and evidences from pre-clinical studies in human isolated airways poses the question whether combining tiotropium 5 μg with olodaterol 5 μg is the best combination option: tiotropium/olodaterol 5/5 μg has the same efficacy profile of tiotropium/olodaterol 5/2 μg, and it is less effective than tiotropium/olodaterol 5/10 μg. Furthermore, tiotropium/olodaterol 5/2 μg, 5/5 μg, and 5/10 μg combinations are generally characterized by the same safety profile. Indeed tiotropium/olodaterol 5/5 μg is effective and safe in COPD, but a different development strategy based on solid data obtained from human isolated airways would have driven towards a better-balanced FDC to be tested in Phase III RCTs. Accurate bench-to-bedside plans are needed also in the development of triple combination therapies for asthma and COPD, in which the presence of an ICS in the formulation may further modulate the beneficial interaction between the LABA and the LAMA.

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Keywords: Asthma; COPD; Drug development; Human isolated airways; LABA/LAMA combination; Respiratory; Synergy; Triple therapy

Key Summary Points

Dual bronchodilation therapy is the cornerstone for the treatment of most COPD patients.

LABAs and LAMAs should be balanced at isoeffective concentrations to elicit synergistic effect.

Not all the currently marketed LABA/LAMA FDCs are correctly balanced.

Tiotropium/olodaterol 5/5 μg FDC is effective and safe, but a development strategy based on data from human isolated airways would have driven towards a better-balanced combination to be tested in Phase III RCTs.

COMMENTARY

The current recommendations for the pharmacological treatment of chronic obstructive pulmonary disease (COPD) are pushing towards the use of triple combination therapy based on the combination of an inhaled corticosteroid (ICS) associated with two bronchodilator agents characterized by different mechanisms of action [1]. However, to date the dual bronchodilation therapy remains the cornerstone for the treatment of most COPD patients [2].

Several evidences resulting from ex vivo studies [3–8] indicate that combining a long-acting β_2 adrenoceptor agonist (LABA) with a long-acting muscarinic antagonist (LAMA) induces appreciable synergistic bronchorelaxant effect at the level of both medium and small bronchi, by potentiating the airway smooth muscle (ASM) relaxation $\approx$ 25% compared to the additive effect and $\approx$ 45% compared to the effect induced by the monocomponents [9].

Interestingly, such a significant synergistic interaction is prevalent when the medications are administered at low and isoeffective concentrations. These two pivotal conditions put the rationale to reduce and balance the doses of each single bronchodilator agent included into the currently marketed LABA/LAMA fixed-dose combination (FDC) formulations in order to increase the safety profile of dual bronchodilation therapy by maintaining an effective level of bronchorelaxation in COPD patients [10].

In order to better elucidate the importance of the concept that different classes of bronchodilators must be combined at "low and isoeffective concentrations", we have performed a post hoc analysis by calculating the Combination Index, the core of the Unified Theory in drug combination studies [11], from data of four pre-clinical studies [3–6] that assessed the interaction between LABAs and LAMAs. Briefly, in these experiments the relaxant effect of LABAs and LAMAs was tested on the contractile tone induced by cholinergic activation in human isolated bronchi. The bronchodilator agents were administered alone and in combination at different concentrations eliciting the same level of ASM relaxation, the isoeffective concentrations. The graphical representation of the Combination Index indicates that at low, nanomolar concentrations the pharmacological interaction between the LABA/LAMA combinations aclidinium/formoterol (Fig. 1a), glycopyrronium/indacaterol (Fig. 1b), tiotropium/olodaterol (Fig. 1c), and umeclidinium/vilanterol (Fig. 1d), elicited strong to very strong synergistic bronchorelaxant effect.

Since 1990s it is well known that the optimal condition to induce pharmacological synergy is to administer the drugs at isoeffective concentrations [12]. However, although the investigated bronchodilator agents were administered at concentrations eliciting the same bronchorelaxant effect, it is evident from the graphs shown in Fig. 1 that the most favourable concentration-ratio between the LABAs and LAMAs necessary to optimize the synergistic bronchorelaxant effect may vary considerably across the different LABA/LAMA combinations. In other words, each LABA/LAMA combination is characterized by a specific range of concentration-ratio at which the drug mixture may induce appreciable synergistic interaction.

This is an important assumption that supports the use of preclinical studies in isolated

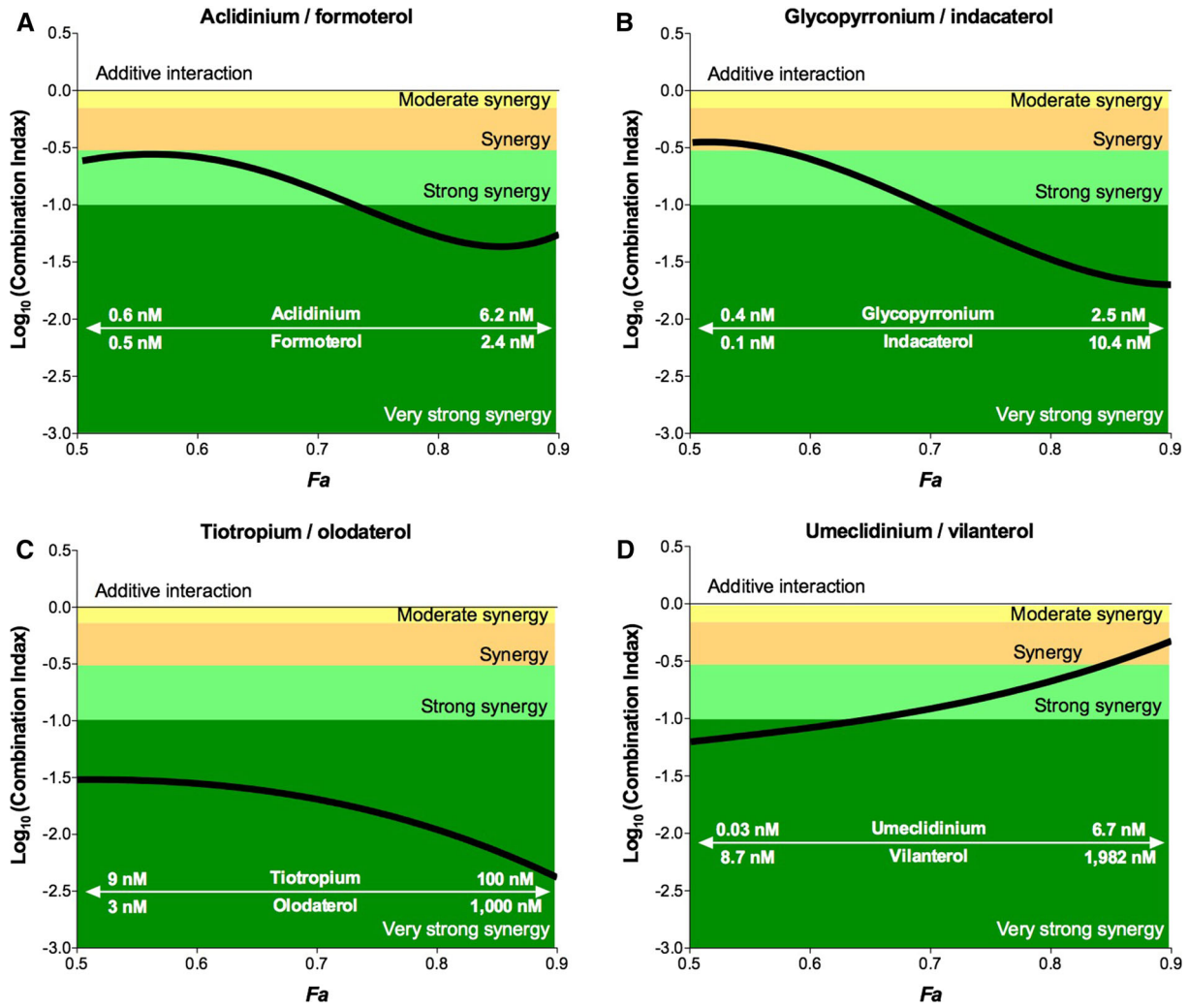

Fig. 1 Graphical representation of Unified Theory analysis via logarithmic combination index plot for aclidinium/formoterol (**a**), glycopyrronium/indacaterol (**b**), triotropium/olodaterol (**c**), and umeclidinium/vilanterol (**d**) combinations. The drugs were administered in combinations at isoeffective concentrations in human medium isolated airways in which ASM contractile tone was induced by the activation of cholinergic pathway. The fraction affected (Fa) indicates the percentage of bronchorelaxant effect, where 0.5 is 50% and 1 is 100%. ASM: airway smooth muscle

airways to correctly identify the best concentration-ratio between the monocomponents, which only then should be further investigated in randomized controlled trials (RCTs). Indeed, such an approach represents the most rationale bench-to-bedside way to correctly develop LABA/LAMA FDCs that can provide real clinical benefits compared to the effects of single bronchodilator therapy.

In the last years there has been increasing interest in producing solid pre-clinical data on the bronchorelaxant synergy between LABAs and LAMAs [3–6], between different bronchodilator agents and ICSs [13, 14], and between mixed phosphodiesterase inhibitors and specific bronchodilators [15, 16]. Paradoxically, most of the pre-clinical investigations on LABA/LAMA combinations have been carried out, either independently [6, 17, 18] or under the support of the Drug Companies [3–5], after the regulatory approval of the FDCs. As a result, it has been demonstrated that in some of the

currently marketed LABA/LAMA FDCs the monocomponents were not adequately balanced, with the bronchorelaxant effect mainly due to the action of the LAMA, with the lack of any synergistic interaction detected not only in ex vivo studies but also in RCTs [6, 19].

Recently, Maltais and colleagues [20] published a Phase II dose-finding RCT to determine the dose-ratio of tiotropium/olodaterol combination vs. tiotropium alone in moderate-to-severe COPD patients. Correctly, the authors stated that during the clinical development of a FDC of drugs, the best practice suggests to perform dose-finding investigations to determine the optimal dose of each component [20]. Making available to the scientific community just in 2019 the results of a Phase II study of the LABA/LAMA FDC tiotropium/olodaterol 5/5 μg approved in both EU and US since 2015 appears at least peculiar. However, data reported by Maltais and colleagues [20] are of interest and worth of considerations that go beyond those discussed in their paper.

First of all, tiotropium plus olodaterol administered at 5/2 μg and at the currently approved dose 5/5 μg produced a numerical, but not statistically significant, increase in trough forced expiratory volume in 1 s (FEV_1) compared to tiotropium 5 μg. Only adding olodaterol 10 μg to tiotropium 5 μg elicited a significant improvement in trough FEV_1 vs. tiotropium 5 μg. After 4 weeks of treatment, tiotropium/olodaterol 5/10 μg enhanced 57 mL trough FEV_1 compared to tiotropium 5 μg, a borderline value when considering the minimal clinically important difference (MCID) with respect to active comparators (MCID: > 60 mL) [21]. Conversely, the effects of tiotropium/olodaterol 5/2 μg and 5/5 μg on trough FEV_1 were far from the MCID (27 mL and 33 mL, respectively).

Furthermore, contrary to what the authors stated [20], there was no dose–response effect when increasing doses of olodaterol were combined with tiotropium. In fact, the impact of tiotropium/olodaterol 5/2 μg on trough FEV_1, peak FEV_1, and $FEV_{1(0–3\ h)}$ was generally equivalent to that induced by tiotropium/olodaterol 5/5 μg. Conversely, adding olodaterol 10 μg to tiotropium 5 μg induced a substantial improvement in trough FEV_1, peak FEV_1, and $FEV_{1(0–3\ h)}$ with respect to tiotropium/olodaterol 5/2 μg and 5/5 μg.

Although these findings appear unexpected by a functional point of view, they can be explained by considering the data on the pharmacological characterization of the interaction between tiotropium and olodaterol in human isolated airways [3]. In fact, looking at the concentration–response curves generated by ex vivo investigations, tiotropium was characterized by greater potency and more inclined hill-slope than olodaterol [3]. Moreover, while tiotropium completely relaxed human ASM, olodaterol produced ≈ 75% relaxant effect [3]. These pharmacological evidences clearly indicate that, in order to adequately balance the concentration-ratio between tiotropium and olodaterol and satisfy the concept of isoeffectiveness, the amount of olodaterol included in the FDC should have been greater than that of tiotropium.

Effectively, the RCT of Maltais and colleagues [20] provides the strong evidence that the best combination is that in which tiotropium 5 μg is combined with olodaterol 10 μg, and not with olodaterol 5 μg. Therefore, along with data from pre-clinical studies, it seems that tiotropium should have been combined with olodaterol at a ≈ 1:2 concentration ratio.

The findings of Maltais and colleagues [20] are consistent with those of a previous unpublished study (NCT00720499), in which 4 weeks of treatment with tiotropium/olodaterol 5/2 μg produced the same improvement in trough FEV_1 when compared with of tiotropium/olodaterol 5/5 μg (57 mL and 55 mL, respectively). Another RCT [22] indicated that there was little difference in trough FEV_1 when tiotropium 5 μg is combined with either olodaterol 5 μg or 10 μg (155 mL and 163 mL, respectively), but we cannot omit that tiotropium/olodaterol 5/10 μg produced a substantial improvemend in $FEV_{1(0–6)}$ when compared with tiotropium/olodaterol 5/5 μg (342 mL and 307 mL, respectively) [22]. Overall, there is no doubt that tiotropium/olodaterol 5/10 μg guarantees a greater and more sustained bronchodilation than that induced by tiotropium/olodaterol 5/5 μg.

Table 1 Effect of adding a LABA to a LAMA on FEV_1 in patients with COPD

	Change from baseline in FEV_1 (mL)	Delta effect vs. LAMA alone	Time-point	Proved synergy in vivo in COPD patiens	References
Aclidinium 400 μg	67 ± 27	–	Peak effect at day 1: 240 min post dose	NA	[17]
Aclidinium/formoterol 400/12 μg	138 ± 16	+ 70 ± 16	Peak effect at day 1: 120 min post dose	Yes	
Glycopyrronium 50 μg	239 ± 33	–	Peak effect at day 1: 90 min post dose	NA	[18]
Glycopyrronium/ indacaterol 50/150 μg	255 ± 41	+ 17 ± 41	Peak effect at day 1: 90 min post dose	No at peak effect; yes at 15 min (± 75 ± 31 mL)	
Tiotropium 5 μg	241 ± 22	–	Peak effect at week 4: 120 min post dose	NA	[20]
Tiotropium/olodaterol 5/2 μg	330 ± 27	+ 89 ± 27	Peak effect at week 4: 120 min post dose	Data not available	
Tiotropium/olodaterol 5/5 μg	327 ± 25	+ 86 ± 25	Peak effect at week 4: 180 min post dose	Data not available	
Tiotropium/olodaterol 5/10 μg	381 ± 24	+ 140 ± 24	Peak effect at week 4: 180 min post dose	Data not available	
Umeclidinium 62.5	91 ± 92	–	Data on trough FEV_1 at day 15	NA	[6]
Umeclidinium/ vilanterol 62.5/25 μg	168 ± 91	+77 ± 91	Data on trough FEV_1 at day 15	No	

COPD chronic obstructive pulmonary disease, *FEV_1* trough forced expiratory volume in 1 s, *LABA* long-acting β_2 adrenoceptor agonist, *LAMA* long-acting muscarinic antagonist, *NA* not applicable

Considering the dual bronchodilator combinations included in this commentary, adding a LABA to a LAMA in patients with COPD induces an overall clinically relevant increase in FEV_1 of ≈ 65 mL, when the drug mixtures were administered at the currently approved doses (Table 1). Nevertheless, and remarkably, when olodaterol 10 μg is added to tiotropium 5 μg the the improvement in FEV_1 even doubled, regardless of any synergistic interaction proved for this combination in vivo in COPD patients (Table 1).

Therefore, taken together the pre-clinical and clinical evidences, it is unclear what is the rational for combining tiotropium 5 μg with olodaterol 5 μg: tiotropium/olodaterol 5/5 μg has the same efficacy profile of tiotropium/olodaterol 5/2 μg, and it is less effective than tiotropium/olodaterol 5/10 μg. Finally, but not less important, looking at the frequency of adverse events (AEs) and serious AEs reported in the ClinicalTrial.gov database (i.e. NCT01040403, NCT00720499, and NCT00696020), tiotropium/olodaterol 5/2 μg, 5/5 μg, and 5/10 μg combinations are generally characterized by the same safety profile. Specifically, considering the European Medicine Agency [EMA] ranking, the pooled analysis of the frequency of all the AEs, both serious and not serious, was common (9%) by combining tiotropium 5 μg with olodaterol administered at 2 μg, or 5 μg or 10 μg (www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/01/WC500137021.pdf).

Considering that the study of Maltais and colleagues [20] was designed when tiotropium Respimat® was already licensed in several countries at the dose of 5 μg, and olodaterol was still in development, with the Phase III trials ongoing with 5 μg and 10 μg, in our opinion tiotropium/olodaterol 5/10 μg FDC should have been the best balanced formulation to be marketed, as it optimizes the synergistic interaction between the monocomponents leading to clinically appreciable improvement in lung function.

Indeed, several factors such as the pharmacokinetic (PK) characteristics, safety profile, and devices might be important for the choice of final doses in RCTs. In this respect, to date all the LABA/LAMA FDCs considered in this post hoc analysis where well characterized by a PK viewpoint (NCT02969317) [23–25], an in-deep meta-analysis is currently available concerning their safety profile [26], and data are also available on the role of inhaler devices in optimizing the dual bronchodilation therapy [27]. In any case, these factors are outside the topic of this commentary and require specific and extensive considerations.

Concluding, tiotropium/olodaterol 5/5 μg FDC remains an effective and safe pharmacological treatment for most COPD patients [28–30]. Perhaps a different development strategy based on solid data obtained from human isolated airways, and not from not-translational animal models of drugs interaction [20, 31], would have driven towards a better-balanced LABA/LAMA FDC to be tested in Phase III RCTs. Accurate bench-to-bedside plans are needed also in the development of triple combination therapies for asthma and COPD, in which the presence of an ICS in the formulation may further modulate the beneficial interaction between the LABA and the LAMA in the formulation [21, 32].

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Data Availability. the datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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