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Editorial

Triple Therapy in Asthma

Triple terapia en asma

The classic treatment for asthma consists of varying doses of inhaled corticosteroids (ICSs) combined with long-acting beta-2 agonists (LABAs). Only relatively recent have clinicians begun to add long-acting antimuscarinics (LAMAs) in the treatment of people without persistent airflow obstruction, although this approach is perfectly logical from a conceptual perspective. The parasympathetic nervous system plays an important role in the modulation of bronchial muscle tone and in the glandular secretion of bronchial mucus,[1] and research has established that ICSs, LABAs, and LAMAs exert a synergistic effect.[2] Clinical practice guidelines and consensus statements provide inconsistent recommendations on how to use LAMAs in the management of asthma. However, all state that triple therapy should precede biologic therapy, and many consider triple therapy a viable option in moderate persistent asthma.[3–6] Some documents go further and suggest using LAMAs in combination with medium-dose ICSs without LABAs.[7] Research has shown that triple therapy administered in multiple devices has demonstrated benefits in reducing the time to the first severe exacerbation and providing additional bronchodilation in asthma patients with persistent airflow limitation.[8] This could be a therapeutic alternative to stepping up ICS dose in uncontrolled patients,[9] although no publications have addressed this comparison directly. Several clinical trials have investigated single-device triple therapy with different doses of ICS (ARGON, CAPTAIN, IRIDIUM, TRIMARAN and TRIGGER).[10–13] Their results corroborate previous findings on the benefits of triple therapy and provide additional data favoring the use of LAMAs in people with asthma (Table 1). However, there are no published studies comparing different combinations of single-device triple therapy. Meta-analyses and post-hoc studies of the above-mentioned phase 3 trials have attempted to identify predic-

Table 1
Randomized controlled trials of triple therapy using a single inhaler device in asthma.

Trial	Population	Interventions	Summary
TRIMARAN NCT02676076 Virchow et al.[13]	Adult patients ($N = 1155$), with uncontrolled asthma on medium strength of ICS + LABA	Extrafine BDP/FF/GLY 100/6/12.5 mg vs extrafine BDP/FF 100/6 mg 2 inh. b.i.d. (total daily dose: 400/24/50)	Compared with the BDP/FF group, week 26 predose FEV1 improved in the BDP/FF/GLY group by 57 mL (95% CI 15–99; $p = 0.0080$) with reductions in the rate of moderate and severe exacerbations of 15% (rate ratio 0.85, 95% CI 0.73–0.99; $p = 0.033$)
TRIGGER NCT02676089 Virchow et al.[13]	Adult patients ($N = 1437$), with uncontrolled asthma with double therapy high doses of ICS + LABA	BDP/FF/GLY 200/6/10 mg vs BDP/FF 200/6 mg 2 inh. b.i.d. (total daily dose: 800/24/50)	Compared with the BDP/FF group, week 26 predose FEV1 improved in the BDP/FF/GLY group by 73 mL (26–120; $p = 0.0025$) with reductions in the rate of moderate and severe exacerbations of 12% (0.88, 0.75–1.03; $p = 0.11$)
IRIDIUM Kerstjens et al.[12]	Adults with symptomatic asthma despite medium/high-dose ICS–LABA	MF/IND/GLY 80/150/50 mg or 160/150/50 mg o.d. vs MF/IND 160/150 mg; 320/150 mg o.d. vs FP/SLM 500/50 mg b.i.d.	At week 26, medium and high-dose MF/IND/GLY showed superior improvement in trough FEV1 versus corresponding doses of MF/IND. Improvements in trough FEV1 were greater than for high-dose FP/SLM (119 mL [85–154]; $p < 0.001$)
ARGON Gessner et al.[10]	Adult patients ($N = 1426$) with symptomatic asthma despite treatment with medium or high-dose ICS–LABA	MF/IND/GLY 80/150/50 mg or 160/150/50 mg o.d. vs FP/SLM 500/50 mg b.i.d. + TIO 5 mg o.d.	MF/IND/GLY high- and medium-dose o.d. via a single inhaler were non-inferior to FP/SLM high-dose b.i.d. + TIO o.d. via 2 inhalers for AQLQ. MF/IND/GLY high-dose o.d. improved lung function, asthma control and health status vs FP/SLM high dose + TIO, while MF/IND/GLY medium dose had comparable efficacy but at a corresponding lower steroid dose
CAPTAIN Lee et al.[11]	Adults ($N = 2439$) with inadequately controlled asthma despite ICS/LABA	F/VI/UMEC 100/25/62.5 mg vs F/VI 100/25 mg F/VI/UMEC 200/25/62.5 mg vs F/VI 200/25 mg	Adding UMEC improved lung function but did not lead to a significant reduction in moderate and/or severe exacerbations

Table adapted from Mahay et al. (2025) under the terms of the Creative Commons CC BY 4.0 license. Source: Mahay G, Zysman M, Guibert N, et al. Long-acting muscarinic antagonists (LAMA) in asthma: What is the best strategy? Respir Med Res. 2025;87:101157. https://doi.org/10.1016/j.resmer.2025.101157.
Abbreviations: b.i.d., twice daily; BDP, beclomethasone dipropionate; F, fluticasone furoate; FF, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; MF, mometasone furoate (Elocon Cream); o.d., once daily; SLM, salmeterol; TIO, tiotropium bromide; UMEC, umeclidinium bromide; VI, vilanterol.

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tive factors for efficacy, and while their conclusions vary, this may be due to methodological disparities across the studies, including differing definitions of exacerbation.[2]

The three LAMAs available on the market are tiotropium bromide, glycopyrronium bromide, and umeclidinium bromide. All are available as monotherapy or as fixed-dose dual therapy in combination with LABAs, while glycopyrronium bromide and umeclidinium bromide are also available as triple therapy in a single inhaler (with high doses of mometasone, high doses of budesonide, or medium-to-high doses of beclomethasone). For asthma, approved treatments containing LAMAs are tiotropium monotherapy, mometasone/indacaterol/glycopyrronium, beclomethasone/formoterol/glycopyrronium, and fluticasone furoate/vilanterol/umeclidinium.[2] The latter combination is only marketed in the USA.

Although few cost-effectiveness studies have been published on triple therapy in asthma, there is a large and consistent body of evidence supporting its efficacy and safety, and some real-world evidence suggests better adherence with single-inhaler triple therapy compared to multiple inhalers in asthma, although supporting data remain limited.[14] However, the real-life implementation of triple therapy falls far short of current recommendations. Bagnasco and colleagues administered 340 questionnaires to pulmonologists, allergists, and pediatricians from 47 countries to analyze the factors that influenced the use of triple therapy in routine clinical practice. Almost all specialists agreed on the need to optimize inhaled therapy before starting monoclonal antibodies; however, when asked whether inhaled triple therapy should be used in conjunction with monoclonal antibody therapy, only 42.6% agreed, while 39.2% disagreed and 18.2% neither agreed nor disagreed. According to the authors, this disparity is likely due to the lack of precise and uniform criteria in current guidelines on whether to escalate to triple therapy from medium-dose or high-dose ICSs/LABAs, on how to adjust ICS dose within triple therapy, and on how to better endotype patients who would benefit from starting biologic therapy early rather than using triple therapy as an intermediate step.[15] In one Delphi study conducted in Spain,[16] the expert panelists agreed that asthma symptoms are better controlled by increasing ICS dose versus adding a LAMA, but that adding a LAMA to medium doses of ICS/LABA is preferable in people with airflow obstruction, osteoporosis, or a history of oropharyngeal mycosis. The panelists also agreed that single-device triple therapy should not be used as MART (maintenance and reliever therapy), and that it improves therapeutic adherence and efficacy, is cost-effective, has ecological benefits, and facilitates ICS dose modification without LAMA–LABA dose modification.

Despite the abundant evidence in favor of triple therapy for asthma, knowledge gaps hinder its use in clinical practice in many situations. The evidence suggests it would be useful to reach an expert consensus on the administration of triple inhaled therapy in a single device for the treatment of asthma.

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Conflicts of interest

We declare that there is no conflict of interest related to this work.

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