The use of triple therapy in asthma. The GEMA-FORUM V task force

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According to the Spanish Asthma Management Guide (GEMA) and the Global Initiative for Asthma (GINA) guidelines, the preferred treatment for steps 4 and 5 is the combination of inhaled corticoids (ICS) at medium or high doses, respectively, and long-acting beta$_2$-agonist (LABA) [1, 2]. In patients with uncontrolled asthma despite medium or high-dose ICS/LABA, triple therapy including ICS (medium or high doses), LABA, and long-acting muscarinic antagonist (LAMA) can be considered, which has been shown to improve lung function and reduce exacerbations, but without clinically significant changes in symptoms or quality of life [3-12]. A meta-analysis showed that medium or high-dose ICS/LABA/LAMA achieved a 17% reduction in severe exacerbations [9]. However, other study reported that severe exacerbation rate was lower in patients receiving high-dose ICS/LABA than with low/medium-dose ICS/LABA/LAMA [11]. In fact, guidelines recommend increasing the dose of ICS before considering adding LAMA. So the position of triple therapy in these therapeutic steps is not clear. For this reason, the GEMAFORUM task force proposed a Delphi consensus to know the opinion of experts on issues in which there is no evidence, or it is scarce, regarding the use of LAMA and triple therapy in clinical practice.

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After reviewing the most recent literature and 13 discussion meetings, a scientific committee of 3 coordinators and 13 experts in pulmonology and allergology proposed a questionnaire of 62 items grouped into three topics: 1) role of LAMA in asthma; 2) Early indication: triple therapy at medium doses of ICS; and 3) Late indication: triple therapy at high doses of ICS. Following the same Delphi methodology described previously [13], and explained in the supplementary material, the items were sent to a panel of 85 experts in asthma from all over Spain (53 pulmonologists and 32 allergists) to give their degree of agreement. It is important to note that the Delphi consensus is an indirect observation of the real prescription situation, and does not include the patient's perspective or the general practitioner positioning.

After two rounds, a consensus was reached on 45 items: 41 in agreement (66.1%) and 4 in disagreement (6.5%). Table 1 shows the items with the highest degree of agreement. The results of the 62 items are shown in the supplementary material.

Regarding the role of LAMA in asthma, panelists agreed that LAMA can replace LABA in combination with ICS when LABA is poorly tolerated or contraindicated, but they disagreed that "LAMA cannot replace LABA in combinations with ICS being only an additional drug". Panelists also agreed that LAMA have a good safety profile and a better cardiovascular safety profile than LABA. However, they also agreed that LAMA should be administered with caution in patients with narrow-angle glaucoma, prostatic pathology, or urinary retention. Panelists agreed that LAMA are especially indicated in patients with asthma and bronchiectasis, chronic airflow obstruction, frequent coughing, or mucosal hypersecretion. Indeed, to choose the best treatment, panelists agreed to determine the phenotype of asthma patients, regardless of severity, as neutrophilic phenotype is associated with a better response to LAMA. In concordance to this, they

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disagreed “to identify responding patients to LAMA without phenotyping”. Of note, they did not reach a consensus with some response criteria, such as bronchial hyperresponsiveness in the methacholine challenge test, obesity-associated asthma, or reversibility in the bronchodilator test. With a high rate of consensus, panelists agreed that combined ICS/LABA/LAMA in a single device improves therapeutic adherence and treatment efficacy (by ensuring synergy between drugs), is cost-effective, bring ecological benefits (by reducing materials and energy in manufacturing, and reducing waste), and even allow to modify ICS dose. On the other hand, the administration of LAMA in a separate device allows assessment of response to this drug and to add LAMA transiently without modifying the base treatment. Of note that the possible transient use of LAMA in the clinical practice did not reach a consensus.

Regarding the use of medium-dose-ICS/LABA/LAMA, in accordance with guidelines, panelists agreed that stepping-up ICS is more effective than adding LAMA in symptoms control. However, they agreed that adding LAMA to ICS/LABA is preferable to stepping-up ICS in patients with airflow obstruction, osteoporosis, or history of oropharyngeal mycosis. Of note, they agreed that stepping-up to high-dose ICS is preferable than switch to triple therapy for prevention of exacerbations, but they did not reach consensus in the item that stated that stepping-up ICS is preferable to switching to triple therapy. In contrast to previous agreement, panelists did not reach consensus in items that stated that ICS/LABA/LAMA is equally effective as high-dose ICS in preventing exacerbations (regardless of severity). Finally, panelists agreed to assess patient’s inflammatory profile before adding LAMA and that triple therapy is effective in preventing exacerbations when treatment is planned for the long term. However, panelists disagreed that “triple therapy in a single device should be administered after testing response to LAMA in a separate

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device", or "the administration of LAMA in a separate device in elderly patients to avoid the change of the previous inhaler".

Concerning the use of high-dose-ICS/LABA/LAMA, panelists agreed that this treatment has special utility in patients with non-T2 asthma or non-eosinophilic asthma. They considered that the priority response criteria to triple therapy are symptoms control, improvement of quality of life, and decrease of exacerbations, but they did not reach consensus on improving pulmonary function. They also agreed that triple therapy is not recommended in maintenance and reliever therapy (MART) strategy because of the potential adverse events of drug abuse and due to the lack of clinical trials. However, they considered that more comparative studies between ICS/LABA/LAMA versus ICS/LABA with MART strategy are needed. Regarding the stepping-down of ICS in triple therapy, panelists agreed that a single device does not involve an obstacle in controlled patients. They also agreed that the withdrawal of LAMA or the reduction of ICS should be based on the inflammatory patient's profile. Other important agreements included that triple therapy is indicated in smoking patients or prior biologics.

Most of the answers given by the panelists were consistent with the published literature. A relevant point of this consensus was the necessity to characterize patients before receiving treatment. However, it is noteworthy that panelists did not consider one of the best predictors of response to LAMA, such as airflow obstruction, and took into account others with less evidence, such as the inflammatory profile. Although triple therapy is included in clinical guidelines, more studies are still needed to draw solid conclusions, comparing its long-term use with other alternatives.

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Conflict of interest

Vicente Plaza in the last three years received honoraria for speaking at sponsored meetings from AstraZeneca, Chiesi, GlaxoSmithKline, and Novartis; received help assistance to meeting travel from Chiesi and Novartis; act as a consultant for ALK, AstraZeneca, Boehringer Ingelheim, Mundipharma, and Sanofi; and received funding/grant support for research projects from a variety of Government agencies and not-for-profit foundations, as well as AstraZeneca, Chiesi, and Menarini.

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José Ángel Carretero in the last three years has received help assistance to attend congresses, and honoraria for participating as a speaker at meetings or to participate in advisory boards from AstraZeneca, GlaxoSmithKline, Novartis, Boehringer Ingelheim, Chiesi, Gebro, and Sanofi.

Íñigo Ojanguren Arranz declares to have received honoraria in the last three years for participating as a speaker in meetings sponsored by AstraZeneca, Boehringuer-Ingelheim, Chiesi, and Novartis and as a consultant for AstraZeneca, GlaxoSmithKlein, Puretech, and Sanofi. He received financial aid from AstraZeneca, Bial, and Chiesi for congress attendance and has received grants from Sanofi for research projects.

José María Vega Chicote received fees in the past five years as a consultant and as a speaker at meetings sponsored by GlaxoSmithKline, AstraZeneca, Novartis, Teva, Chiesi, Mundipharma, Menarini, Bial, Gebro Pharma, ALK-Abelló, LETI, Stallergenes, Merck, Hal, Allergopharma, Allergy-Therapeutics, and Inmunotek.

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References

1. Guía Española para el Manejo del Asma (GEMA) v5.3 [cited 2023 October 17]. Available from: https://www.gemasma.com/.
2. Global Initiative for Asthma. 2022 GINA Report. Global Strategy for Asthma Management and Prevention [cited 2023 March 31]. Available from: https://ginasthma.org/.
3. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012;367:1198-207.
4. Sobieraj DM, Baker WL, Nguyen E, Weeda ER, Coleman CI, White CM, et al. Association of Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists With Asthma Control in Patients With Uncontrolled, Persistent Asthma: A Systematic Review and Meta-analysis. JAMA. 2018;319:1473-84.
5. Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, et al. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. Lancet. 2019;394:1737-49.
6. Singh D, Virchow JC, Canonica GW, Vele A, Kots M, Georges G, et al. Extrafine triple therapy in patients with asthma and persistent airflow limitation. Eur Respir J. 2020;56.
7. Kerstjens HAM, Maspero J, Chapman KR, van Zyl-Smit RN, Hosoe M, Tanase AM, et al. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. Lancet Respir Med. 2020;8:1000-12.
8. Gessner C, Kornmann O, Maspero J, van Zyl-Smit R, Krull M, Salina A, et al. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON). Respir Med. 2020;170:106021.
9. Kim LHY, Saleh C, Whalen-Browne A, O'Byrne PM, Chu DK. Triple vs Dual Inhaler Therapy and Asthma Outcomes in Moderate to Severe Asthma: A Systematic Review and Meta-analysis. JAMA. 2021;325:2466-79.

doi: 10.18176/jiaci.0975

10. Rogliani P, Ritondo BL, Calzetta L. Triple therapy in uncontrolled asthma: a network meta-analysis of phase III studies. Eur Respir J. 2021;58.

11. Lee LA, Bailes Z, Barnes N, Boulet LP, Edwards D, Fowler A, et al. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. Lancet Respir Med. 2021;9:69-84.

12. Casale TB, Aalbers R, Bleecker ER, Meltzer EO, Zaremba-Pechmann L, de la Hoz A, et al. Tiotropium Respimat(R) add-on therapy to inhaled corticosteroids in patients with symptomatic asthma improves clinical outcomes regardless of baseline characteristics. Respir Med. 2019;158:97-109.

13. Quirce S, Trigueros JA, Ausin P, Munoz Cano R, Ramirez Hernandez M, Gonzalez-Barcala FJ, et al. Role of the different healthcare professionals in the management of asthma patients. The GEMA-FORUM IV task force. J Investig Allergol Clin Immunol. 2022:0.

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Table 1. Items with the highest degree of agreement achieved after the two rounds

Topic 1. Role of LAMA in asthma	**Agreem. (%)**
Experience with the use of LAMAs in COPD confirms that adverse effects are of low incidence and mild in most cases and that, therefore, they have a good safety profile in the treatment of asthma.	96.5
LAMAs are especially indicated in asthma patients with chronic airflow obstruction.	91.8
Combined ICS/LABA/LAMA treatment in a single device improves therapeutic adherence.	95.3
Combined ICS/LABA/LAMA treatment in a single device minimizes the risk of poor technique with respect to the use of multiple devices.	91.8
Topic 2. Early indication: ICS/LABA/LAMA at medium doses of ICS	**Agreem. (%)**
In patients treated with ICS/LABA at medium doses of ICS, adding LAMA is preferable to stepping-up ICS in patients with osteoporosis.	74.1
In patients treated with ICS/LABA at medium doses of ICS, adding LAMA is preferable to stepping-up ICS in patients with a history of oropharyngeal mycosis.	74.1
Triple therapy is effective in preventing exacerbations when treatment is planned for the long term.	73.3
Before adding LAMA to the treatment of asthma, it is recommended to assess the patient's inflammatory profile.	91.8
Topic 3. Late indication: ICS/LABA/LAMA at high doses of ICS	**Agreem. (%)**
The priority response criterion to triple therapy is a decrease in exacerbations.	88.4
Comparative studies between triple therapy versus ICS-LABA with MART strategy are needed.	86.0
It is not recommended to perform triple therapy in MART strategy due to the possible adverse effects of medication abuse.	83.5
Triple therapy can be considered, in most cases, as a step prior to the use of a biologic drug.	95.4

COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; MART: Maintenance and Reliever Therapy.

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