Use of Triple Therapy in Asthma: The GEMA-FORUM V Task Force

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According to the Spanish Asthma Management Guidelines (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 ß2-agonists (LABAs) [1,2]. In patients with uncontrolled asthma despite medium- or high-dose ICS/LABA, triple therapy including ICS (medium or high doses), LABAs, and long-acting muscarinic antagonists (LAMAs) can be considered. This approach has been shown to improve lung function and reduce exacerbations, albeit with no 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, another study reported that the severe exacerbation rate was lower in patients receiving high-dose ICS/LABA than in those receiving low/medium-dose ICS/LABA/LAMA [11]. In fact, guidelines recommend increasing the dose of ICS before considering adding LAMAs. Therefore, 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 areas in which there is no or scarce evidence for the use of LAMAs and triple therapy in clinical practice.

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 comprising 62 items grouped into 3 topics: *1*) The role of LAMAs in asthma; *2*) Triple therapy at medium doses of ICS as an early indication; and *3*) Triple therapy at high doses of ICS as a late indication. Following the Delphi methodology described above [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 determine their degree of agreement. It is important to note that the Delphi consensus is an indirect observation of the real prescribing situation and does not include the patient's perspective or the position of the general practitioner.

After 2 rounds, a consensus was reached on 45 items: 41 in agreement (66.1%) and 4 in disagreement (6.5%). The Table 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 LAMAs in asthma, the panelists agreed that a LAMA can replace the LABA in combination with ICS when the LABA is poorly tolerated or contraindicated, but they disagreed, stating that a LAMA cannot replace a LABA in combinations where the ICS is only an additional drug. The panelists also agreed that LAMAs have a good safety profile and a better cardiovascular safety profile than LABAs. However, they also agreed that LAMAs should be administered with caution in patients with narrow-angle

Table. Items With the Highest Degree of Agreement Achieved After the 2 Rounds.

Topic 1. Role of LAMAs in asthma	Agreement, %
Experience with the use of LAMAs in COPD confirms that adverse effects are infrequent 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 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	**Agreement, %**
In patients treated with ICS/LABA at medium doses of ICS, adding LAMAs is preferable to stepping up ICS in patients with osteoporosis.	74.1
In patients treated with ICS/LABA at medium doses of ICS, adding LAMAs 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 LAMAs to the treatment of asthma, it is recommended to assess the patient's inflammatory profile.	91.8
Topic 3. Late indication: ICS/LABA/LAMAs at high doses of ICS	**Agreement, %**
The priority criterion for response to triple therapy is a decrease in exacerbations.	88.4
Studies comparing triple therapy with ICS/LABA and MART are needed.	86.0
Triple therapy is not recommended in MART owing to the possible adverse effects of medication overuse.	83.5
Triple therapy can be considered, in most cases, as a step prior to the use of a biologic drug.	95.4

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting ß2-agonist; LAMA, long-acting muscarinic antagonist; MART, maintenance and reliever therapy.

glaucoma, prostatic disease, or urinary retention. The panelists agreed that LAMAs are especially indicated in patients with asthma and bronchiectasis, chronic airflow obstruction, frequent coughing, and mucosal hypersecretion. Indeed, to choose the best treatment, the panelists agreed to determine the phenotype of asthma patients, regardless of severity, as the neutrophilic phenotype is associated with a better response to LAMAs. Accordingly, they disagreed, refusing to identify patients responding 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, and reversibility in the bronchodilator test. With a high rate of consensus, the panelists agreed that combining ICS/LABA/LAMA in a single device improves adherence and efficacy (by ensuring synergy between drugs), is cost-effective, brings ecological benefits (by reducing materials and energy in manufacturing and reducing waste), and even makes it possible to modify the ICS dose. On the other hand, the administration of LAMAs in a separate device enables the response to this drug to be assessed and LAMAs to be added transiently without modifying the base treatment. Of note, no consensus was reached with respect to the possible transient use of LAMAs in clinical practice.

Regarding the use of medium-dose ICS/LABA/LAMA, in accordance with guidelines, the panelists agreed that stepping up ICS is more effective for symptom control than adding LAMAs. However, they agreed that adding LAMAs to ICS/LABA is preferable to stepping up ICS in patients with airflow obstruction, osteoporosis, or a history of oropharyngeal mycosis. Of note, they agreed that stepping up to high-dose ICS is preferable to switching to triple therapy for prevention of exacerbations, although they did not reach a consensus on the item stating that stepping up ICS is preferable to switching to triple therapy. In contrast, panelists did not reach a consensus on items that stated that ICS/LABA/LAMA is equally effective as high-dose ICS in preventing exacerbations (regardless of severity). Finally, the panelists agreed that it was necessary to assess the patient's inflammatory profile before adding LAMAs and that triple therapy is effective in preventing exacerbations when long-term treatment is planned. However, the panelists disagreed with respect to the statements "Triple therapy in a single device should be administered after testing the response to LAMAs in a separate device" and "LAMAs should be administered in a separate device in elderly patients to avoid having to change the previous inhaler".

Concerning the use of high-dose-ICS/LABA/LAMA, the panelists agreed that this treatment is particularly useful in patients with non-T2 asthma or noneosinophilic asthma. They considered that the priority criteria for response to triple therapy are symptom control, improvement in quality of life, and decrease in exacerbations, although they did not reach a consensus on improving pulmonary function. They also agreed that triple therapy is not recommended in maintenance and reliever therapy (MART) because of the potential adverse events of overuse and the lack of clinical trials. However, they considered that more comparative studies between ICS/LABA/LAMA and ICS/LABA with MART are needed. Regarding the stepping-down of ICS in triple therapy, the panelists agreed that a single device does not constitute an obstacle in patients

with controlled disease. They also agreed that withdrawal of LAMAs or reduction of ICS dosage should be based on the patient's inflammatory profile. Other important agreements were that triple therapy is indicated in smokers and patients who have previously received biologics.

Most of the replies given by the panelists were consistent with the published literature. A relevant point of this consensus was the need to characterize patients before prescribing treatment. However, it is noteworthy that the 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, further studies are still needed to draw solid conclusions and compare long-term use with alternatives.

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Conflicts of Interest

In the last 3 years, Vicente Plaza has received the following: honoraria for speaking at sponsored meetings from AstraZeneca, Chiesi, GlaxoSmithKline, and Novartis; travel assistance from Chiesi and Novartis; fees for consultancy from ALK, AstraZeneca, Boehringer Ingelheim, Mundipharma, and Sanofi; and funding/grant support for research projects from a variety of government agencies and not-for-profit foundations, as well as from AstraZeneca, Chiesi, and Menarini.

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In the last 3 years, José Ángel Carretero has received assistance for attending congresses and honoraria for participating as a speaker at meetings or on advisory boards from AstraZeneca, GlaxoSmithKline, Novartis, Boehringer Ingelheim, Chiesi, Gebro, and Sanofi.

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In the past 5 years, José María Vega Chicote received fees 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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