

SUPPLEMENTARY MATERIAL

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

DELPHI CONSENSUS RESULTS

To respond to the items, a unique nine point ordinal Likert-type scale was proposed according to the model developed by UCLA-RAND Corporation (minimum 1, full disagreement; and maximum 9, full agreement). This scale was structured in three groups according to the level of agreement-disagreement of the item: from 1 to 3, interpreted as rejection or disagreement; from 4 to 6, interpreted as no agreement or disagreement; and from 7 to 9, interpreted as expression of agreement or support.

The consensus was reached when two-thirds or more of the respondents scored within the 3-point range (1-3 or 7-9) containing the median. The type of consensus achieved on each item was determined by the median value of the score. There was agreement if the median was ≥ 7 , and there was disagreement if the median was ≤ 3 . When the median score was located between a 4-6 range, the items were uncertain.

Table 1. Results achieved by the experts after the two rounds of Delphi consensus

	Median (IQR)	% agreement	% disagreement
Topic 1. Role of LAMA in asthma			
1. LAMAs can replace LABAs in combinations with ICS in those patients in whom LABAs are poorly tolerated or have contraindications.	8 (2)	71.8	10.6
2. LAMAs can replace LABAs in combinations with ICS in patients with asthma–COPD overlap.	5 (3)	18.8	31.8
3. LAMAs can replace LABAs in combinations with ICS in patients with ischemic heart disease.	7 (3)	54.1	14.1
4. LAMAs cannot replace in any case LABAs in combinations with ICS, being only an additional drug.	3 (3)	15.3	71.8
5. 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.	8 (1)	96.5	1.2
6. LAMAs have a better cardiovascular safety profile than LABAs.	7 (1)	78.8	4.7
7. LAMA have adverse effects, so the risk/benefit balance should be assessed in patients with prostatic pathology or urinary retention.	7 (2)	67.1	12.9
8. LAMAs have adverse effects, so they should be administered with caution in patients with narrow-angle glaucoma.	8 (1)	83.5	2.4
9. LAMAs have adverse effects that do not make them recommended for patients with severe constipation.	4 (3)	10.6	48.2
10. LAMAs provide additional benefit in patients with asthma and bronchiectasis.	7 (1)	88.2	0.0
11. LAMAs are especially indicated in asthma patients with chronic airflow obstruction.	8 (1)	91.8	2.4
12. LAMAs are especially indicated in asthma patients with frequent coughing.	7 (2)	70.6	3.5
13. LAMAs are especially indicated in patients with asthma and mucosal hypersecretion.	8 (1)	80.0	2.4

14. All patients with asthma, regardless of severity, should be phenotyped in order to determine the best treatment.	9 (2)	77.7	9.4
15. A neutrophilic phenotype is associated with a better response to LAMA.	7 (1)	77.7	2.4
16. A high degree of bronchial hyperresponsiveness in the methacholine challenge test is an indicator of good response to LAMA treatment.	6 (2)	49.4	11.8
17. Patients with obesity-associated asthma are good responders to treatment with LAMA.	5 (1)	23.5	13.0
18. A high reversibility in the bronchodilator test is an indicator of good response to LAMA treatment.	6 (2)	47.1	11.8
19. Identification of patients responding to LAMA treatment should be done without phenotyping, as phenotyping is only recommended in severe asthma.	3 (4)	16.5	67.1
20. Combined ICS/LABA/LAMA treatment in a single device improves therapeutic adherence.	9 (1)	95.3	1.2
21. Combined ICS/LABA/LAMA treatment in a single device increases treatment efficacy by ensuring synergy between the drugs.	8 (2)	83.5	1.2
22. Combined ICS/LABA/LAMA treatment in a single device minimizes the risk of poor technique with respect to the use of multiple devices.	9 (1)	91.8	3.5
23. Combined ICS/LABA/LAMA treatment in a single device is cost-effective.	9 (1)	90.6	1.2
24. Availability of the ICS/LABA/LAMA combination in a single device brings ecological benefits by reducing the consumption of materials and energy expenditure used in its manufacture, generating less waste.	9 (1)	91.8	1.2
25. Availability of the ICS/LABA/LAMA combination in a single device reduces the negative impact on carbon footprint.	9 (2)	87.1	1.2
26. Combined ICS/LABA/LAMA treatment in a single device increases the risk of undertreatment with triple therapy in case of poor adherence.	8 (4)	58.8	17.7
27. Some ICS/LABA/LAMA combinations in a single device allow the ICS dose to be modified.	9 (2)	83.5	7.1

28. Administration of LAMA in a separate device allows assessment of the response to this additional treatment.	7 (2)	69.4	9.4
29. Administration of LAMA in a separate device allows LAMA to be added transiently and withdrawn in the short term without modifying the base treatment.	8 (2)	78.8	7.1
30. Transient administration of LAMA is not routine clinical practice in the management of asthma.	3 (5)	32.9	58.8
Topic 2. Early indication: triple therapy with ICS/LABA/LAMA at medium doses of ICS			
31. In patients treated with ICS/LABA at medium doses of ICS, ICS step-up is more effective in symptom control than adding LAMA.	7 (3)	71.8	3.5
32. In patients treated with ICS/LABA at medium doses of ICS, ICS step-up is preferable to switching to triple therapy because triple therapy often involves switching molecules.	5 (3)	38.8	23.5
33. In patients treated with ICS/LABA at medium doses of ICS, adding LAMA is preferable to stepping-up ICS in patients with airflow obstruction.	7 (2)	71.8	8.2
34. In patients treated with ICS/LABA at medium doses of ICS, adding LAMA is preferable to stepping-up ICS in patients with osteoporosis.	7 (2)	74.1	5.9
35. 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.	8 (2)	74.1	5.9
36. In patients treated with ICS/LABA at medium doses of ICS, stepping-up to high-dose ICS is preferable for prevention of exacerbations than switching to triple therapy.	7 (2)	72.9	5.9
37. Triple therapy with ICS/LABA/LAMA is equally effective as high-dose ICS in preventing exacerbations in patients where previous exacerbations have been mild or moderate.	6 (2)	44.7	10.6
38. Triple therapy with ICS/LABA/LAMA is equally effective as high-dose ICS in preventing exacerbations in patients where previous exacerbations have been severe.	5 (3)	12.9	29.4
39. Triple therapy is effective in preventing exacerbations when treatment is planned for the long term.	7 (2)	73.3	3.5

40. Triple therapy in a single device should be administered after testing the response to the addition of LAMA in a device separate from that of ICS/LABA treatment.	2 (2)	14.1	72.9
41. In elderly patients it is recommended to add LAMA in a different device in order to avoid the change of the previous inhaler.	3 (2)	4.7	73.3
42. Before adding LAMA to the treatment of asthma, it is recommended to assess the patient's inflammatory profile.	7 (2)	91.8	4.7
Topic 3. Late indication: triple therapy with ICS/LABA/LAMA at high doses of ICS			
43. Triple therapy has special utility in the treatment of patients with non-T2 asthma.	7 (1)	75.3	8.2
44. Triple therapy has special utility in the treatment of patients with non-esophilic asthma.	7 (2)	68.2	11.8
45. The priority response criterion to triple therapy is symptom control.	8 (1)	79.1	9.3
46. The priority response criterion to triple therapy is improvement in quality of life.	7 (2)	73.3	10.5
47. The priority response criterion to triple therapy is improvement in pulmonary function.	7 (1)	63.5	7.1
48. The priority response criterion to triple therapy is a decrease in exacerbations.	8 (2)	88.4	3.5
49. Comparative studies between triple therapy versus ICS-LABA with MART strategy are needed.	8 (2)	86.0	7.0
50. It is not recommended to perform triple therapy in MART strategy due to the possible adverse effects of medication abuse.	8 (2)	83.5	2.4
51. It is not recommended to perform triple therapy in MART strategy due to the slower bronchodilator response.	2 (4)	10.6	65.9
52. Triple therapy in a single device does not involve an obstacle to stepping-down of high-dose ICS therapy in controlled patients.	8 (1)	78.8	4.7
53. During stepping-down of treatment with LABA/LAMA/ICS at high doses, reduction of ICS to medium doses is preferable to withdrawal of LAMA.	5 (2)	44.7	7.1
54. During stepping-down of treatment with LABA/LAMA/ICS at high doses, withdrawal of	5 (3)	22.4	30.6

LAMA is preferable to reduction of ICS at medium doses.			
55. During stepping-down of treatment with LABA/LAMA/ICS at high doses, withdrawal of LAMA or reduction of ICS should be decided based on the patient's inflammatory profile.	8 (2)	80.2	5.8
56. During stepping-down of treatment with LABA/LAMA/ICS at high doses, withdrawal of LAMA or reduction of ICS should be decided based on lung function.	7 (3)	52.9	12.9
57. During stepping-down of treatment with LABA/LAMA/ICS at high doses, withdrawal of LAMA or reduction of ICS should be decided based on the patient's quality of life.	7 (2)	57.6	14.1
58. Triple therapy in asthma is especially indicated in smoking patients.	7 (1)	78.8	3.5
59. Triple therapy can be considered, in most cases, as a step prior to the use of a biologic drug.	9 (1)	95.4	1.2
60. For the administration of triple therapy in a single device, ultrafine particle devices are preferable.	8 (3)	74.4	3.5
61. Obtaining a visa hinders access to single-device triple therapy for patients with asthma.	8 (3)	69.4	14.1
62. Treatment of asthma with triple therapy in a single device is best suited to patients with severe asthma who prefer the administration schedule every 12 hours.	8 (3)	73.0	5.9

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

Consensus in agreement
Consensus in disagreement
Neither agreement nor disagreement (uncertain)