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ORIGINAL RESEARCH

A Delphi Consensus Document on the Use of Single-Inhaler Fixed-Dose Triple Therapies in COPD Patients

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Introduction: Despite the evidence provided by clinical trials, there are some uncertainties and controversies regarding the use of triple inhaled therapy. With the aim of evaluating clinical practice in specialized respiratory units, a Delphi consensus document was implemented on the use of single-inhaler fixed-dose triple therapies after 1 year of use in Spain.

Methods: A scientific committee of COPD experts defined a thematic index, guided a systematic literature review and helped design the Delphi questionnaire. This was sent to the other 45 COPD experts between April and June 2019. Agreement/disagreement on 58 statements was tested in two rounds using a Likert scale. Replies were classified as a consensus when ≥80% of the panelists agreed; a majority when a degree of agreement of ≥66% was reached; and divergence if agreement was <66%.

Results: After two rounds, 44.44% of the statements reached consensus, 14.81% reached majority and 40.74% were divergent. Panelists agreed that escalating from double bronchodilation should be phenotype-based and aim to prevent exacerbations but not for improving symptoms. The addition of an antimuscarinic to inhaled corticosteroids combinations achieves improvement in lung function, symptoms and exacerbation prevention. Main safety concerns included the increased risk of pneumonia as compared to bronchodilator therapies, with similar cardiovascular effects. There was no consensus agreement on patient type response based on blood eosinophil counts or obstruction severity.

Conclusion: The low degree of consensus among panelists may reflect the complexity of severe COPD management. The information provided here may be useful to clinicians implementing personalized medicine for COPD patients.

Keywords: chronic obstructive pulmonary disease, LABA/LAMA, LABA/ICS, bronchodilator agents, inhaled corticosteroids, triple therapy, statements, Delphi consensus

Introduction

Chronic obstructive pulmonary disease (COPD) pharmacological treatments aim to reduce symptoms, reduce the frequency and severity of exacerbations.[1,2] The current inhaled pharmacologic treatments for COPD comprise long-acting bronchodilators (LABD), including long-acting β2 adrenergic (LABA) and long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS). The combinations of these drugs have demonstrated clinical benefits for patients. Therefore, different single-inhaler fixed-dose combinations (FDC) are available. For more severe patients, triple therapy combinations, consisting of the addition of a LABA, a LAMA and an ICS, have been

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proposed in current recommendation documents.[1,2] This combination may be given in multiple inhalers; or as FDC, in a single inhaler.[3]

Single-inhaler FDC triple therapy has been available since September 2018 and to date, several clinical trials have shown that it is beneficial compared with monotherapy and double therapies improving efficacy regarding lowering exacerbations and hospitalization rate.[4,5] Clinical benefits have also been reported when using FDC triple therapy compared to tiotropium.[6] In addition to the scientific evidence, in recent months it is beginning to gain clinical experience in its use since its commercialization. According to the current recommendation guidelines, triple therapy can be used in high risk patients with not very well-controlled exacerbations with two drugs and in severe cases of asthma-COPD overlap;[1] as well as in patients who develop further exacerbations or with persistent breathlessness or exercise limitation on LABA/ICS therapy.[2]

Despite the results reported in the clinical trials, there is still disagreement and confusion among the scientific community on its practical use, mainly due to the uncertainty in situations not addressed in clinical trials. In this context, this Delphi consensus document provides information regarding the practical use of FDC triple therapy in specialized respiratory units for COPD patients. The document takes into account the available evidence and the experts' opinion after 1 year of use in Spain, while attempting to facilitate the decisions for clinical practice.

Methods

Governance

This is a document that uses a Delphi methodology comprising two rounds. A scientific committee was constituted, composed by a coordinator and six members with renowned expertise in COPD. The scientific committee was responsible for decision-making and, based on the results of the systematic review, created the Delphi questionnaire and modified it before the second round.

Fifty-one experts, who were not members of the scientific committee, were invited to participate as panelists in the Delphi questionnaire, based on their competence in the management of COPD and conforming the expert panel. The scientific committee prepared the list of participants by reviewing the list of Spanish pulmonologists who participate in the SEPAR national congress as chairs in COPD sessions, on the editorial board of the Spanish journal *Archivos de Bronconeumologia* with COPD articles and by the publications of Spanish members in PubMed related to COPD. Later this list was refined looking for national representativeness by regions. In order to validate the experience of the experts in COPD, all participants were required to answer three questions regarding their clinical and research expertise in COPD: 1) Is COPD your main area of interest?; 2) How long (years) is your experience in COPD patients management?; 3) How many COPD patients approximately do you visit monthly? No approval was required by any ethics committee, since it is a study based on a Delphi process gathering expert opinions without patient participation.

Questionnaire Design

In order to establish the relevant areas regarding the use of triple therapy in patients with stable COPD to be covered with the document, a thematic index (annex) was defined by the scientific committee in a kick-off virtual meeting, held on September 20, 2018. Based on the thematic index, a non-exhaustive systematic review of the literature was performed through Pubmed and an evidence document was generated to synthesize the results from the selected studies. Based on the thematic index and with the help of the evidence document, the scientific committee proposed statements to be included in the Delphi questionnaire, which were agreed and validated through a teleconference based on the scientific committee criteria. The validated questionnaire consisted of 48 statements divided into 10 sections covering the efficacy of FDC triple therapy vs other therapies (efficacy of FDC triple therapy vs LABA/LAMA, efficacy of FDC triple therapy vs LABA/ICS, efficacy of FDC triple therapy vs open triple therapy), safety of FDC triple therapy vs other therapies (general safety of FDC triple therapy, safety of FDC triple therapy vs LABA/LAMA; safety of FDC triple therapy vs LABA/ICS; safety of FDC triple therapy vs open triple therapy); treatment with FDC triple therapy; devices; and costs. The responses regarding the degree of agreement were given using a Likert scale (degrees 1–5, where 1 means completely disagree and 5 completely agree).

Consensus Process

The consensus process was carried out using a Delphi method comprising two rounds.[7] The Delphi technique is a reliable prospective process that permits us to obtain the experts' perception in a specific field and expresses the agreement level reached among them, through their anonymous answers. In round 1, members of the expert panel

were asked to express their degree of agreement with the 48 statements and their answers were analyzed using the following criteria: Agreement (sum of 4 and 5 Likert scale values); neither agreement nor disagreement (NAND; value 3 in Likert scale); disagreement (sum of 1 and 2 values). According to this, the scientific committee defined consensus when ≥80% of the panelists coincided with the same agreement category; majority when ≥66% of them coincided and divergence when <66% of the panellists coincided with the same agreement category. For round 2 of the Delphi process, the statements which reached consensus in the first round were not included. For this round, each answer in divergence or majority was analyzed, in order to decide if they should be more specific or reformulated. Following this, some statements were reformulated to improve understandability and increase the agreement percentage in the second round.

Results

Forty-five panelists completed both round 1, comprising 48 statements, and round 2 (45 statements) of the Delphi questionnaire. Eighteen items were modified before the second round in order to improve clarity. The 45 members included in the final panel were distributed homogeneously over 16 provinces in Spain. In reply to the questions regarding their expertise, most of the participants replied COPD was their main area of interest (42 out of 45) and had more than 10 years of experience managing COPD (41 out of 45). Regarding the patients visited per month, 14 panelists visited more than 100 patients per month, whereas 23 of them visited between 51 and 100 and 8 of them visited less than 50 patients per month.

The distribution of agreements in the two rounds is shown in Figure 1. Altogether, after the two rounds, the panelists had provided their degree of agreement with 54 statements (the ones that reached consensus in round 1 plus all the statements of round 2). Of these, 24 items (44.44%) reached consensus, whereas 8 items (14.81%) reached majority agreement and discrepancy was reached in 22 items (40.74%).

Efficacy of FDC Triple Therapy vs Other Therapies

The statements regarding FDC triple therapies vs LABA/LAMA are shown in Table 1, section a. Out of the 12 statements, three of them achieved consensus, one of these being consensus in disagreement, and two of them majority, whereas the panel showed divergence in seven of them. Two new questions (5b and 9b) were added in round 2 with clarification purposes, and statement 6 was replaced by two new more specific statements (6a and 6b). The main consensus messages were an agreement for items 3 and 7, and a disagreement for item 4.

For the group of statements which sought to compare FDC triple therapy vs LABA/ICS, 7 out of 10 statements achieved consensus, two of them majority and discrepancy was reached in three of them. It should be noted that two new statements were added to the second round in order to clarify the statements of the round 1. Also, question 15 was replaced with two new statements that were consulted

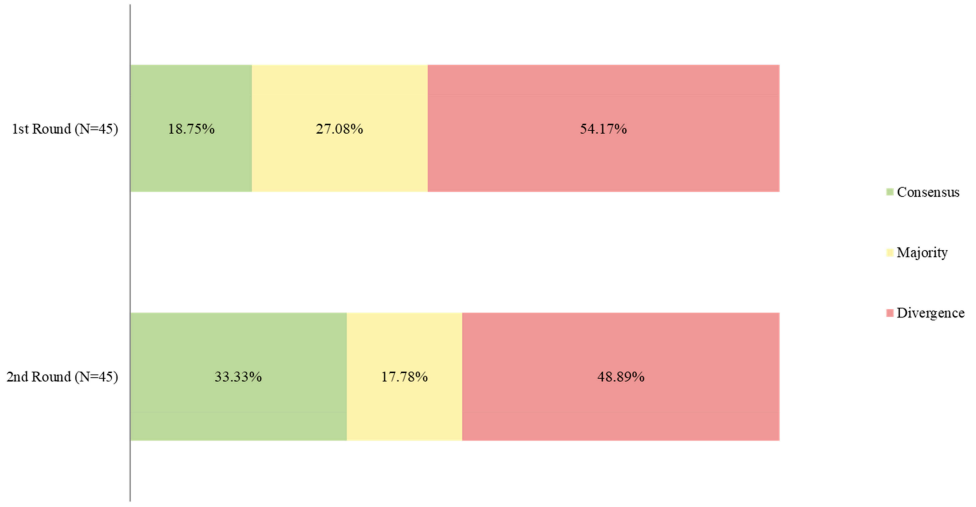

Figure 1 Results of the degree of agreement among the panelists after the 1st and 2nd Delphi rounds. (N) number of panelists that participated in the Delphi round.

Table 1 Results of the Degree of Agreement Among the Panelists with the Statements Regarding Efficacy of Single-Inhaler Fixed Triple Therapy vs LABA/LAMA, LABA/ICS and Open Triple Therapy After the two Delphi Rounds

#	Statement	% Agreement	Round*	Final Results
a. Efficacy of single-inhaler fixed triple therapy vs double therapy LABA/LAMA				
1	In a non-exacerbator COPD patient, with eosinophilia ≥300, single-inhaler fixed triple therapy is indicated before dual LABA/LAMA.	55.56% Disagreement	2	Divergence
2	When deciding to use single-inhaler fixed triple therapy vs dual LABA/LAMA therapy, the COPD phenotype of the patient is taken into account.	91.11% Agreement	1	Consensus
3	Single-inhaler fixed triple therapy is more effective than dual LABA/LAMA therapy to improve the pulmonary function	44.44% Agreement	2	Divergence
4	Single-inhaler fixed triple therapy is more effective than dual LABA/LAMA therapy to improve dyspnea in symptomatic patients (CAT>10), independently of FEV_1 and of the number of previous exacerbations.	80.00% Disagreement	2	Consensus
5a	Single-inhaler fixed triple therapy significantly improves the health-related quality of life (measured by the St. George's Respiratory Questionnaire (SGRQ)) compared to dual LABA/LAMA therapy.	62.22% Agreement	2	Divergence
5b	In your clinical practice, the single-inhaler fixed triple therapy improves the health-related quality of life when compared with dual LABA/LAMA therapy.	46.67% Agreement	2	Divergence
6a	Single-inhaler fixed triple therapy is more effective than dual LABA/LAMA therapy to reduce the number of exacerbations in a patient with COPD and FEV_1 < 50%	62.22% Agreement	2	Divergence
6b	Single-inhaler fixed triple therapy is more effective than dual LABA/LAMA therapy to reduce the number of exacerbations in a patient with COPD and frequent exacerbations.	77.78% Agreement	2	Majority
7	In COPD patients treated with dual LABA/LAMA therapy hospitalized because of one severe or two moderate exacerbations, the treatment must be escalated to single-inhaler fixed triple therapy independently of the number of eosinophils.	84.44% Agreement	2	Consensus
8	In COPD patients treated with dual LABA/LAMA therapy hospitalized because of one severe or two moderate exacerbations and with a number of eosinophils <100, the treatment must be escalated to single-inhaler fixed triple therapy	51.11% Agreement	2	Divergence
9a	Single-inhaler fixed triple therapy improves COPD patients' survival compared to dual LABA/LAMA therapy	44.44% NAND	2	Divergence
9b	Single-inhaler fixed triple therapy improves survival of COPD patients with frequent exacerbations compared to dual LABA/LAMA therapy	66.67% Agreement	2	Majority
b. Efficacy of single-inhaler fixed triple therapy vs dual LABA/ICS therapy				
10	In a COPD patient receiving monotherapy LABA or LAMA it is correct to escalate to single-inhaler fixed triple therapy skipping dual LABA/ICS therapy	62.22% Disagreement	2	Divergence
11	Single-inhaler fixed triple therapy is more effective than dual LABA/ICS therapy to improve pulmonary function	84.44% Agreement	1	Consensus
12	Single-inhaler fixed triple therapy is more effective than dual LABA/ICS therapy to improve the symptoms	95.56% Agreement	2	Consensus
13	Single-inhaler fixed triple therapy is more effective than dual LABA/ICS therapy to improve dyspnea in symptomatic patients (CAT>10), independently of FEV_1 and of the number of previous exacerbations	95.56% Agreement	2	Consensus
14a	Single-inhaler fixed triple therapy significantly improves the health-related quality of life (measured by the SGRQ questionnaire) compared with dual LABA/ICS therapy	95.56% Agreement	2	Consensus
14b	In your clinical practice, single-inhaler fixed triple therapy significantly improves health-related quality of life compared to dual LABA/ICS therapy	75.56% Agreement	2	Majority
15a	Single-inhaler fixed triple therapy is more effective than dual LABA/ICS therapy reducing the number of exacerbations in a COPD patient with FEV_1 < 50%	84.44% Agreement	2	Consensus
15b	Single-inhaler fixed triple therapy is more effective than dual LABA/ICS therapy reducing the number of exacerbations in a COPD patient with frequent exacerbations	93.33% Agreement	2	Consensus
16	In COPD patients treated with dual LABA/ICS therapy hospitalized because of one severe or two moderate exacerbations, the treatment must be escalated to single-inhaler fixed triple therapy, independently of the number of eosinophils	80.00% Agreement	2	Consensus
17	In COPD patients treated with dual LABA/ICS therapy hospitalized because of one severe or two moderated exacerbations and with a number of eosinophils < 100, the treatment must be escalated to single-inhaler fixed triple therapy	68.89% Agreement	2	Majority

(*Continued*)

Table 1 (Continued).

#	Statement	% Agreement	Round*	Final Results
18a	Single-inhaler fixed triple therapy improves survival in COPD patients compared to dual LABA/ICS therapy	57.78% Agreement	2	Divergence
18b	Single-inhaler fixed triple therapy improves survival in COPD patients with frequent exacerbations compared to dual LABA/ICS therapy	62.22% Agreement	2	Divergence
c. Efficacy of single-inhaler fixed triple therapy				
19	Based on your clinical experience, currently efficacy differences exist among the known single-inhaler fixed triple therapies	57.78% NAND[2]	2	Divergence
20	Single-inhaler fixed triple therapy is more effective than open triple therapy in improving the pulmonary function	46.67% NAND[2]	2	Divergence
21	Single-inhaler fixed triple therapy is more effective than open triple therapy in improving dyspnea	64.44% Agreement[2]	2	Divergence
22	Single-inhaler fixed triple therapy is more effective than open triple therapy in improving quality of life	62.22% Agreement[2]	2	Divergence
23	Single-inhaler fixed triple therapy is more effective than open triple therapy in reducing the number of moderate and severe exacerbations	42.22% Disagreement[2]	2	Divergence
24	In the subgroup of patients suffering >1 moderate-severe exacerbation in the 12 previous months, the single-inhaler fixed triple therapy is more effective than open triple therapy in reducing the number of moderate-severe exacerbations	44.44% Agreement[2]	2	Divergence

Notes: The final results were determined considering the degree of agreement among the panellists meant consensus: ≥80%; majority ≥66%; or divergence (<66%). NAND: neither agreement nor disagreement. *Indicates the round where the degree of agreement shown was reached. In bold those words changed from round one to round two.

in round 2 (Table 1, section b). Consensus on agreement was for items 11–14a, both 15 and 16.

In reply to the six statements of the group which compared efficacy of fixed triple therapy vs open triple therapy, none of them achieved consensus or majority, being all divergent among the participants (Table 1, section c).

Safety of FDC Triple Therapy vs Other Therapies

The answers of the panelists to these statements are shown in Table 2. All items reached a consensus except for item 25. The first question was formulated regarding the general safety of FDC triple therapy compared to others, and the replies given by the panelists were divergent. The question was reformulated in round 2, however, still divergence was found (Table 2, section a).

The second group of statements, about the safety of FDC triple therapy vs LABA/LAMA therapy comprised three statements, all achieving consensus by the panelists. Two of the consensuses reached were in disagreement with the statement, whereas only one was of agreement with it (Table 2, section b).

The two statements comparing the safety of FDC with the LABA/ICS therapy achieved consensus, one in agreement with the statement and the other one in disagreement (Table 2, section c). Finally, all three statements about the safety of FDC triple therapy compared to open triple therapy also achieved consensus (two in agreement, one in disagreement) among the panelists (Table 2, section d).

Treatment with FDC Triple Therapy in Specific Patient Types

Of the five statements of this group of statements, three of them achieved majority, two of them majority in disagreement and one of them in agreement, whereas panelists had divergent replies in two of them (Table 3). The statements 35, 36 and 37 were reformulated to improve understanding.

Devices for FDC Triple Therapy

Eight statements were consulted among the panelists, who achieved consensus in six of them, of which one was in disagreement, and discrepancy in two (Table 4).

Costs Associated to FDC Triple Therapy vs Other Therapies

This group included two statements, one of them achieving agreement in majority and the other one discrepancy among the panelists with neither agreement nor disagreement. The statement 48 was reformulated to increase specificity and avoid different interpretations (Table 5).

Table 2 Results of the Degree of Agreement of the Panelists with the Statements Regarding Safety of Single-Inhaler Fixed Triple Therapy vs LABA/LAMA, LABA/ICS and Open Triple Therapy After the two Delphi Rounds

#	Statement	% Agreement	Round*	Final Results
a. General safety of single-inhaler fixed triple therapy				
25	Based on your clinical experience, currently differences exist in the safety profile of the different known single-inhaler fixed triple therapies	62.22% Disagreement[2]	2	Divergence
b. Safety of single-inhaler fixed triple therapy vs dual LABA/LAMA therapy				
26	Single-inhaler fixed triple therapy has the same risk of producing pneumonia than dual LABA/LAMA therapy	86.67% Disagreement[2]	2	Consensus
27	Single-inhaler fixed triple therapy produces similar cardiovascular adverse effects to those produced by dual LABA/LAMA therapy	82.22% Agreement[1]	1	Consensus
28	Single-inhaler fixed triple therapy produces similar local adverse effects to those produced by dual LABA/LAMA therapy	82.22% Disagreement[2]	2	Consensus
c. Safety of single-inhaler fixed triple therapy vs dual LABA/ICS therapy				
29	Single-inhaler fixed triple therapy causes more pneumonia cases than dual LABA/ICS therapy	80.00% Disagreement[1]	1	Consensus
30	Single-inhaler fixed triple therapy produces similar cardiovascular adverse effects to those produced by dual LABA/ICS therapy	88.89% Agreement[2]	2	Consensus
d. Single-inhaler fixed triple therapy vs open triple therapy				
31	Single-inhaler fixed triple therapy causes more pneumonia cases than open triple therapy	86.67% Disagreement[1]	1	Consensus
32	Single-inhaler fixed triple therapy produces similar cardiovascular adverse effects to those produced by open triple therapy	82.22% Agreement[1]	1	Consensus
33	Single-inhaler fixed triple therapy produces similar local adverse effects to those produced by open triple therapy	84.44% Agreement[1]	1	Consensus

Notes: The final results were determined considering the degree of agreement among the panelists: consensus ≥80%; majority ≥66%; or divergence (<66%). NAND: neither agreement nor disagreement. *Indicates the round where the degree of agreement shown was reached. In bold are words changed from round one to round two.

Discussion

The present study provides the cumulative opinion of 45 experts on important statements regarding the use of FDC triple therapy vs other available treatments in the management of COPD patients. The experts' replies are based on their clinical practice and the scientific evidence. According to the results, the experts diverge on their perception of efficacy of FDC triple therapy vs LABA/LAMA, whereas their level of agreement is higher when compared to LABA/ICS. Safety is perceived as similar among the different therapies. Regarding treatment with FDC triple therapy, the experts' views are generally aligned with the current recommendations, and they perceive cost-effectiveness in FDC triple therapy vs LABA/ICS but not vs LABA/LAMA.

The incorporation of new drugs and inhaler devices to the treatment paradigm of COPD constitutes a great opportunity to improve the management of COPD patients, and, although current guidelines provide general recommendations, there can be confusion and disagreement among healthcare providers in some aspects regarding the use of FDC triple therapy.[8]

Among the statements where the experts diverged most were around the efficacy of FDC triple therapy vs LABA/LAMA in terms of quality of life and reduction of the number of exacerbations in patients with COPD and FEV1 < 50%. This is probably because the scientific evidence available is not enough to establish a firm conclusion on this topic,[5,9,10] which has been also shown in a recently published systematic review.[11] The differences existing among the molecules, including the different results in lung function, symptoms or exacerbations,[11] could also have influenced the replies since the molecules to be compared were not specified in the statements. Regarding the COPD patients with frequent exacerbations, the agreement, without reaching consensus, in the higher effectivity of FDC triple therapy vs LABA/LAMA, is in agreement with the systematic reviews by Zheng et al[10] and López-Campos et al[11] that showed that

Table 3 Results of the Degree of Agreement Among the Panelists with the Statements Regarding Treatment with Single-Inhaler Fixed Triple Therapy in Specific Patient Types After the two Delphi Rounds

#	Statement	% Agreement	Round*	Final Results
34	In high risk, non-exacerbator COPD patients, with a number of eosinophils > 300, single-inhaler fixed triple therapy is indicated as starting therapy	73.33% Disagreement	2	Majority
35	In patients with more than wo exacerbations and a number of eosinophils < 100, single-inhaler fixed triple therapy is indicated as starting therapy	75.56% Disagreement	2	Majority
36	In patients with very severe obstruction (FEV_1 <30%) who do not present exacerbations, single-inhaler fixed triple therapy is indicated as starting therapy	42.22% Disagreement	2	Divergence
37	The use of single-inhaler fixed triple therapy needs to be indicated by the pneumologist	62.22% Disagreement	2	Divergence
38	To make the decision of using single-inhaler fixed triple therapy, it must be taken into account if the patient has pneumonia precedent	75.56% Agreement	2	Majority

Notes: The final results were determined considering the degree of agreement among the panelists: consensus ≥80%; majority ≥66%; or divergence (<66%). NAND: neither agreement nor disagreement. *Indicates the round where the degree of agreement shown was reached. In bold are those words changed from round one to round two.

Table 4 Results of the Degree of Agreement Among the Panelists with the Statements Regarding the Different Device Options After the two Delphi Rounds

#	Statement	% Agreement	Round*	Final Results
39	The Ellipta® device has shown a lesser number of critical errors compared to other devices that use triple therapy	93.33% Agreement[2]	2	Consensus
40	The fine particle with Modulite® technique has shown bigger pulmonary deposit in peripheral airways than other devices that use triple therapy	82.22% Agreement[2]	2	Consensus
41	The pulmonary deposit originated by the single-inhaler fixed triple therapy is similar to the one originated by the dual LAMA/LABA therapy	51.11% Agreement[2]	2	Divergence
42	The pulmonary deposit originated by the single-inhaler fixed triple therapy is similar to the one originated by the dual LABA/ICS therapy	60.00% Agreement[2]	2	Divergence
43	Single-inhaler fixed triple therapy leads to a higher decrease in the number of critical errors than open triple therapy	93.33% Agreement[1]	1	Consensus
44	Single-inhaler fixed triple therapy leads to higher adherence to the treatment than open triple therapy	93.33% Agreement[1]	1	Consensus
45	The administration pattern of single-inhaler fixed triple therapy every 12 hours is more effective than every 24 hours pattern	84.44% Disagreement[2]	2	Consensus
46	The administration pattern of single-inhaler fixed triple therapy every 24 hours improves the adherence compared to every 12 hours pattern.	84.44% Agreement[2]	2	Consensus

Notes: The final results were determined considering the degree of agreement among the panellists: consensus ≥80%; majority ≥66%; or divergence (<66%). NAND: neither agreement nor disagreement. *Indicates the round where the degree of agreement shown was reached.

triple therapy significantly reduced moderate or strong exacerbations rate vs LABA/LAMA. Interestingly, and although the current guidelines do not support this statement, the consensus reached in the escalation from LABA/LAMA to FDC triple therapy independently of the number of eosinophils in patients hospitalized because of severe to moderate exacerbations, may have been based on the IMPACT study,[4] where the annual rate of moderate or severe exacerbations was lower with triple therapy than with either double-therapy combination, regardless of eosinophil level,[4] Interestingly, the panelists may also have taken into account the results of the IMPACT study when reaching a majority consensus on the statement that FDC triple therapy improves survival of COPD patients with frequent exacerbations compared to LABA/LAMA therapy.

A higher degree of agreement was achieved among panelists on the efficacy of FDC triple therapy vs LABA/ICS therapy, as evidenced from the FULFIL[12] and TRILOGY trials.[13] According to the results of IMPACT[4] and FULFIL,[12] the panelists also agreed on the higher

Table 5 Results of the Degree of Agreement Among the Panelists with the Statements Regarding Costs of the Diverse Therapeutic Options for the COPD Patients After the two Delphi Rounds

#	Statement	% Agreement	Round*	Final Results
47	In patients with symptomatic COPD, the single-inhaler fixed triple therapy is more cost-effective than the dual LABA/ICS therapy	75.56% Agreement	2	Majority
48	In high-risk patients according to the GesEPOC definition, the single-inhaler fixed triple therapy is more cost-effective than the dual LABA/LAMA therapy	53.33% NAND	2	Divergence

Notes: The final results were determined considering the degree of agreement among the panelists: consensus ≥80%; majority ≥66%; or divergence (<66%). NAND: neither agreement nor disagreement. *Indicates the round where the degree of agreement shown was reached. In bold are those words changed from round one to round two.

efficacy of FDC triple therapy vs LABA/ICS in reducing exacerbations when the COPD patients have FEV1<50% or frequent exacerbations. In the KRONOS study, however, no significant impact was reported.[14] Regarding escalating from monotherapy to triple therapy, the panelists reply in accordance with the GOLD guides,[2] agreeing that double therapy should precede triple. The disagreement regarding survival improvement may occur because only one of the combinations has shown improved survival and in previous studies similar survival rates amongst treatments has been found.[5,9,10,12,13]

Regarding FDC triple therapy vs open triple therapy, the divergence observed in all statements is due probably to the fact that some panelists based their opinion on their own clinical practice whereas the reference for others was the available scientific evidence from the literature, which shows no inferiority in the FEV1 and no significant differences in exacerbation rate, dyspnea and quality of life in fixed triple therapy compared to open triple therapy.[6,15]

In relation to safety, the opinion (although not consensus) of the panelists on the lack of difference among FDC triple therapies versus LABA/ICS is consistent with the clinical trials[4,12,14] and Zheng et al,[10] who observed that triple therapy was not associated with an increase in the risk of adverse events compared to LABA/ICS. Regarding differences with LABA/LAMA, several studies[4,14] and the systematic review by Zheng et al,[10] have shown the safety profile of FDC triple therapy is different than that of LABA/LAMA in pneumonia risk. These results may have supported the consensus of the panelists. In the TRIBUTE study, the pneumonia risk was reported to be similar in patients of each treatment arm.[5] On the other hand, the response of the panelists regarding the cardiovascular adverse effects produced by FDC triple therapy or LABA/LAMA is consistent with the results of the TRIBUTE and KRONOS studies.[5,14] The panelists' response is also consistent with several studies and a systematic review when considering that adverse effects related to FDC triple therapy are similar to those of open triple therapy.[6,10,15]

The majority of panelists disagreed on whether to use FDC as the starting therapy in specific patients' profiles. This is in accordance with the current GOLD document, which recommends escalation to triple therapy in patients who continue to exacerbate or have persistent breathlessness or exercise limitation while on LABA/ICS.[2] Also, the Spanish GesEPOC guidelines recommend using triple therapy in high-risk patients whose exacerbations are not controlled with 2 LABD or a LABD/ICS combination.[1]

The experts reached consensus on the observation that the device Ellipta® has demonstrated less critical errors than other devices used for triple therapy and that the metered dose inhaler with Modulite® technique has demonstrated higher pulmonary deposit in peripheral airways than other devices used for triple therapy, which was highlighted as an advantage in a Spanish consensus.[16] Instead, it is of interest that when the devices were not specified in the statement, the replies varied among the experts and consensus was not achieved. The same was observed when the experts were consulted on whether FDC triple therapy originates a pulmonary deposition pattern similar to that of LABA/LAMA and LABA/ICS. Similarly, the panelist agree that there are reductions of critical errors with FDC vs open triple therapy as is supported by studies[17–19] that highlight the potential improvement in adherence when using fixed triple therapy. In this regard, it is remarkable that consensus was reached on the higher adherence of FDC triple therapy vs open triple therapy, despite the lack of clinical evidence. The higher adherence with 24-hours pattern compared to 12-hours pattern was also agreed by the panelists. Likewise, the results show that they perceive no differences in efficacy in these two dosing patterns, even though there is no data proving it.

Regarding the perception of higher cost-effectiveness of the FDC triple therapy versus dual LABA/ICS therapy, it is possibly due to the differences in efficacy and safety

existing among both therapies, although little is known about it to date. This is in agreement with a post hoc analysis of the FULFIL study, where fixed triple therapy appeared to reduce the economic burden and the use of medical resources compared with LABA/ICS.[20] On the contrary, it is interesting that agreement was not achieved regarding the cost-effectiveness of FDC triple therapy compared to LABA/LAMA, probably due to the limited clinical and scientific evidence in this specific area.

Although there is growing evidence for a clinical benefit of triple therapy over monotherapy or LABA/ICS treatment, more results on real-world trials would be very beneficial, as well as the results of ongoing clinical trials comparing triple therapy to LABA/LAMA combination.

Strengths and Limitations

To our knowledge, this is the first study providing experts' opinion on the use of the FDC triple therapy for the treatment of COPD. This study has been carried out using a solid, well-known and rigorous methodology based on the Delphi technique.[21] This methodology has permitted the exchange of knowledge and opinion and the reaching of a consensus when there is uncertainty or limited evidence, and when there is not a uniform approach in clinical practice. However, our study also has some limitations: the Delphi technique only provides qualitative results, resulting from the punctuation on the degree of agreement of the panelists, based on the evidence, their clinical practice and experience. These recommendations must be taken as experts' opinion, acknowledging that the sample of panelists is not representative of the whole specialist population. Finally, panelists were all pulmonologists showing their opinions and practice in specialized respiratory units. It is possible that a panel composed of primary care physicians could have given other results that have not been explored with the present design.

Conclusions

This study provides insights on the use of the FDC triple therapy regarding its efficacy, safety, treatment, devices, and costs, based on the consensus of a 45-expert panel. The results of this Delphi consensus are in general in agreement with international guidelines both in the indication of triple therapy and in that its use in a single inhaler is safe, and is at least as effective with potential additional benefits improving adherence, inhaler management, and cost compared to other forms of inhaled therapy for COPD. The results show that there is a general perception of the benefits of FDC triple therapy over the double therapy LABA/ICS regarding efficacy in improving dyspnea, pulmonary function, quality of life and reducing exacerbations. The effects are perceived to be higher against ICS/LAB than LABA/LAMA therapy. Likewise, safety is perceived to be quite similar among the different options. The divergence found among panelists reveals the complexity of COPD and the need for further scientific evidence to help them to better position the FDC combination in relation to its efficacy, safety and its use in COPD patients. In addition, the discrepancies also reveal that high risk COPD are a heterogeneous and complex group, and the choice of the best treatment depends on many variables that were not always represented in the statements. It is therefore of great importance to continue working towards personalized medicine in COPD treatment.

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Author Contributions

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