Special article

“Correct Use of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease”: A Consensus Document☆

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A B S T R A C T

Introduction: Indications for inhaled corticosteroids (IC) in combination with long-acting bronchodilators (LABD) are well defined in clinical practice guidelines. However, there are some doubts about their efficacy and safety. The aim of this document is to establish an expert consensus to clarify these issues.

Method: A coordinator group was formed, which systematically reviewed the scientific evidence with the aim of identifying areas of uncertainty about the efficacy of ICs, the adverse effects associated with their use and criteria for withdrawal. Their proposals were submitted to a panel of experts and the Delphi technique was used to test the level of consensus.

Results: Twenty-five experts participated in the panel, and consensus was reached on the use of IC in the mixed chronic obstructive pulmonary disease (COPD)-asthma phenotype and in frequent exacerbators, and on not using IC in association with LABD for improving lung function in COPD. There was no general consensus on restricting the use of IC to prevent adverse effects. The panel did agree that IC withdrawal is feasible but should be undertaken gradually, and patients who have discontinued must be evaluated in the short term.

Conclusions: Consensus was reached regarding the indication of IC in mixed COPD-asthma and frequent exacerbator phenotypes. The potential for adverse effects must be taken into consideration, but there is no consensus on whether limiting use is justified. The withdrawal of ICs was uniformly agreed to be feasible.

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Documento de Consenso “Uso adecuado de los corticoides inhalados en la enfermedad pulmonar obstructiva crónica”

R E S U M E N

Introducción: Las indicaciones de los corticoides inhalados (CI) asociados a broncodilatadores de larga duración (BDLD) están bien definidas en las guías de práctica clínica. Sin embargo, existen áreas de incertidumbre acerca de su eficacia y seguridad. El objetivo de este documento es establecer un consenso de expertos acerca de estas áreas.


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The members of the Working Group “Consensus document on the appropriate use of inhaled corticosteroids in COPD” listed in Appendix A.

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Introducción

La enfermedad obstructiva crónica de los pulmones (EPOC) es altamente prevalente. Los datos españoles se basan en el estudio EPISCAN y sugieren que afecta a 10.2% de los adultos mayores de 60 años, comparado con el 4% de los adultos mayores de 60 años en el mundo.1,2 Es la tercera causa de muerte en España.3

Los consensos españoles (GesEPOC) recomiendan el uso de broncodilatadores (LABD) como tratamiento de primera línea, cada vez más combinado con otras drogas farmacológicas (long-acting beta-agonistas [LABA] y long-acting muscarinic antagonists [LAMA]), reservando los LABA+inhalados corticoesteroïdes (IC) para exacerbaciones frecuentes con FEV1 inferior a 60% o con IC de uso exclusivo.4

Numerosas revisiones y observaciones en diferentes contextos han demostrado el uso de ICs exclusivas o combinadas con LABD en pacientes con EPOC.10 En algunas ocasiones, los pacientes con EPOC tienen exacerbaciones frecuentes, y alrededor del 20% de los pacientes tienen exacerbaciones frecuentes.4

En el contexto de la EPOC, el objetivo del uso de ICs es mejorar la calidad de vida de los pacientes. La conveniencia del uso de ICs en pacientes con exacerbaciones frecuentes se ha discutido en múltiples consensos, como el de 2013-2014 y 2015-2016.10,12,13 En estos consensos se decidieron distintas estrategias de tratamiento, pero no existe consenso sobre cómo manejar las exacerbaciones de EPOC.

Material and Methods

Este consenso se desarrolló a través de un grupo de profesionales que participaron en el tratamiento y la investigación del EPOC de acuerdo con el uso de ICs en EPOC. Se seleccionaron de manera consensuada las actividades de investigación en el EPOC, la participación activa en los consensos, así como la implicación en las sociedades científicas dedicadas al EPOC. Se llevó a cabo una revisión sistemática de la literatura sobre el uso de ICs en el EPOC.

El consenso se desarrolló en dos fases: la primera fase se realizó mediante el método Delphi para decidir el uso de ICs en el EPOC. En la segunda fase, se decidió el uso de ICs en el EPOC. En ambas fases, se obtuvieron resultados consistentes en la mayoría de los casos.

En resumen, este consenso se desarrolló a través de un grupo de profesionales con experiencia en el tratamiento y la investigación del EPOC de acuerdo con el uso de ICs en EPOC. Se seleccionaron de manera consensuada las actividades de investigación en el EPOC, la participación activa en los consensos, así como la implicación en las sociedades científicas dedicadas al EPOC. Se llevó a cabo una revisión sistemática de la literatura sobre el uso de ICs en el EPOC.
Table 1

<table>
<thead>
<tr>
<th>Statements on the Efficacy of ICs in Stable COPD, With the Percentage of Agreement in the First and Second Rounds, and the Consensus Result.</th>
<th>% Agreement in 1st round</th>
<th>% Agreement in 2nd round</th>
<th>Final results</th>
</tr>
</thead>
<tbody>
<tr>
<td>In general, I would not add an IC to a LABA to improve a COPD patient’s state of health</td>
<td>83</td>
<td>52</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>In general, I would not add an IC to a LABA to improve a COPD patient’s dyspnea</td>
<td>87.5</td>
<td>80</td>
<td>Majority</td>
</tr>
<tr>
<td>In general, I would not add an IC to a LABA to improve a COPD patient’s lung function</td>
<td>76</td>
<td>92</td>
<td>Consensus</td>
</tr>
<tr>
<td>In general, I would not add an IC to a LABA to avoid lung function decline determined by FEV1</td>
<td>71</td>
<td>64</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>In general, I would add an IC to a LABD to reduce the number of exacerbations in a COPD frequent exacerbator (≥2 episodes/year) with FEV1 &lt;50%</td>
<td>83.5</td>
<td>100</td>
<td>Consensus</td>
</tr>
<tr>
<td>In general, I would add an IC to a LABD in a COPD patient with a severe exacerbation</td>
<td>58</td>
<td>52</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>In general, I would add an IC to a LABD in a COPD frequent exacerbator, irrespective of the level of severity determined by FEV1</td>
<td>54</td>
<td>92</td>
<td>Consensus</td>
</tr>
<tr>
<td>In general, I would add an IC to a LABD in a COPD patient with frequent infectious exacerbations</td>
<td>37.5</td>
<td>52</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>In general, I would add an IC to a LABD in a patient with mixed COPD-asthma phenotype</td>
<td>100</td>
<td></td>
<td>Consensus</td>
</tr>
</tbody>
</table>

To analyze the data, the coordinating group collected all responses, transferred them to a Microsoft Office Excel spreadsheet (2010), and calculated the voting percentages for each block, as established above.

Results

Twenty-seven physicians were invited to take part in the voting rounds (including pulmonologists, internal medicine and primary care specialists). Of these, 25 (92.6%) finally submitted their level of agreement with the statements.

Clinical Efficacy of Inhaled Corticosteroids Combined With Long-Acting Bronchodilators

The results of the 2 rounds of voting on this area of interest are presented in Table 1. In the first round of questions, consensus was reached on the use of ICs combined with LABD in the treatment of mixed COPD-asthma phenotype, with 100% agreement. In a second round of voting, consensus was obtained for 3 more statements referring to (1) the unsuitability of IC combined with LABDs to improve lung function in COPD patients (92% agreement); (2) combining ICs with LABDs for reducing exacerbations in patients with severe COPD (FEV1 <50%) and frequent exacerbations (100% agreement); and (3) the use of combination IC+LABD in frequent exacerbators, irrespective of the level of severity determined by FEV1 (92% agreement). Most participants in the working group agreed that IC should not be combined with LABD for improving dyspnea (80% agreement).

Table 2

<table>
<thead>
<tr>
<th>Statements on the Side Effects of ICs in Stable COPD, With the Percentage of Agreement in the First and Second Rounds, and the Consensus Result.</th>
<th>% Agreement in 1st round</th>
<th>% Agreement in 2nd round</th>
<th>Final result</th>
</tr>
</thead>
<tbody>
<tr>
<td>I would withdraw IC treatment in a patient on combined LABD+IC with community-acquired pneumonia</td>
<td>17</td>
<td>16</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>I would change my approach when indicating IC+LABD in a COPD patient with a history of previous pulmonary tuberculosis</td>
<td>37.5</td>
<td>16</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>I would change my approach when indicating IC+LABD in a COPD patient with a history of osteoporosis</td>
<td>20</td>
<td>20</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>I would not change my approach when indicating IC+LABD in a COPD patient with a history of diabetes mellitus</td>
<td>72</td>
<td>72</td>
<td>Majority</td>
</tr>
<tr>
<td>I agree that treatment should begin with high dose IC+LABD</td>
<td>16</td>
<td>16</td>
<td>Indeterminate</td>
</tr>
</tbody>
</table>

Adverse Effects of the Use of Inhaled Corticosteroids Combined With Long-Acting Bronchodilators

None of the 5 proposals on adverse effects reached consensus among the participants (Table 2), although the statement on not modifying treatment when prescribing combined ICs+LABD in patients with a history of diabetes achieved a majority vote (72% agreement).

Withdrawal of Inhaled Corticosteroids in Stable Chronic Obstructive Pulmonary Disease

Six questions on the withdrawal of IC in stable COPD (Table 3) were submitted for consensus. Consensus was reached on the feasibility of IC withdrawal (100% agreement) in the first round of voting. In the second round, the statement regarding short-term follow-up after IC withdrawal reached consensus (96% agreement), and the majority (79%) of participants felt that IC withdrawal should be tapered.

Regarding the criteria for indicating withdrawal of IC in stable COPD, consensus was obtained for patients with no exacerbations in the previous 2 years and in the absence of criteria for mixed COPD-asthma phenotype. There was less agreement on withdrawal if the patient did not present a positive bronchodilator test (>200 ml and >12 FEV1 improvement) at the time of the evaluation and in the absence of decline after switching from high to intermediate IC doses. The general conclusion from these results is that IC withdrawal is possible if there is no evidence of mixed COPD-asthma phenotype, no exacerbations in the previous 2 years, and with a
lower level of agreement, in the absence of a positive bronchodilator test and decline after switching from high to intermediate IC doses (Table 4).

**Discussion**

The results of the process identify some areas of uncertainty in which it is difficult to achieve consensus. However, the expert panel is in overall agreement about certain statements.

The working group achieved consensus on the statement that all mixed COPD-asthma phenotype patients should continue to receive IC+LABA, irrespective of their disease severity or number of exacerbations. Although these patients are usually excluded from clinical trials with ICs in COPD, these data are in line with recent reviews showing that patients with a positive bronchodilator test have more chance of reducing exacerbations with the use of ICs, and that the response to ICs in COPD is associated with asthma-like characteristics, such as eosinophilic inflammation or raised levels of nitric oxide in exhaled air (FeNO). The statement that an IC should not be added to a LABA to improve lung function determined by FEV\(_1\) in a COPD patient achieved consensus. This opinion is in line with several recent systematic reviews showing that, while the use of ICs combined with LABAs improves FEV\(_1\), especially in the short term, long-term improvement is more modest (between 5 and 20 ml) and of limited clinical significance.

For statements addressing the use of IC+LABA for reducing exacerbations in frequent exacerbators, the expert group agreed that in both situations (in patients with FEV\(_1\) <50% and irrespective of bronchial obstruction severity), ICs should be used along with LABAs. As might be expected, this is in line with the usual indication of IC+LABA in this situation (frequent exacerbations and severe airflow obstruction) in COPD clinical practice guidelines. It is also consistent with more recent studies showing that this combination can reduce exacerbations in patients with frequent exacerbations and FEV\(_1\) <70%. These data suggest, then, that the effect of ICs is probably not related with the level of severity, but rather with an exacerbator phenotype, particularly if characteristics consistent with the COPD-asthma phenotype are observed.

Questions on the side effects of long-term use of ICs did not achieve consensus, and answers differed widely among the group of experts. This shows, on the one hand, the lack of evidence on the side effects of ICs, and on the other, a lack of understanding of the real impact of these side effects on the COPD population usually seen in the clinical setting.

The expert group reached consensus on the statement that withdrawal of ICs in COPD is feasible. Although the evidence on the withdrawal of ICs is in general limited and very heterogeneous, recent studies support the idea proposed by GesEPOC that IC withdrawal is safe in stable patients with no exacerbations. The best strategy for IC withdrawal has yet to be defined. However, it seems logical that, since exacerbations associated with IC withdrawal tend to occur in the first months after discontinuation, COPD patients in this situation should be followed-up as soon as possible. The expert group agreed that patients discontinuing ICs should be seen in the outpatient clinic shortly after withdrawal. New evidence has shown that tapered withdrawal of ICs in even the most severely affected COPD patient is safe and will not lead to exacerbations in the long-term. However, more studies are needed to characterize patients in whom withdrawal is safe.

Finally, the expert group reached consensus on 2 clinical requirements for IC withdrawal in COPD patient (absence of mixed COPD-asthma phenotype and absence of exacerbations in the previous 2 years). These were the most highly recommended, and a further 2 requirements received a majority vote (absence of positive bronchodilator test and absence of decline after switching from high to intermediate dose ICs). These criteria are intended as

**Table 3**

<table>
<thead>
<tr>
<th>Statement</th>
<th>% Agreement in 1st round</th>
<th>% Agreement in 2nd round</th>
<th>Final result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal of ICs in COPD patients is feasible</td>
<td>100</td>
<td>70</td>
<td>Consensus</td>
</tr>
<tr>
<td>ICs should be withdrawn in a clinically stable, non-COPD-asthma phenotype patient who has gone 1 year without exacerbations</td>
<td>70</td>
<td>56</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>If I have decided to withdraw ICs in a COPD patient, a positive bronchodilator test (&gt;12% and &gt;200 ml) would make me change my approach</td>
<td>71</td>
<td>64</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>IC withdrawal should be tapered</td>
<td>72</td>
<td>79</td>
<td>Majority</td>
</tr>
<tr>
<td>A patient who has discontinued ICs should be evaluated in the short term</td>
<td>79</td>
<td>96</td>
<td>Consensus</td>
</tr>
<tr>
<td>IC withdrawal would justify intensification of bronchodilatation</td>
<td>29</td>
<td>44</td>
<td>Indeterminate</td>
</tr>
</tbody>
</table>

**Table 4**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>% Agreement</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No exacerbations in the previous 2 years</td>
<td>96.1</td>
<td>Recommendable criterion</td>
</tr>
<tr>
<td>No evidence of mixed COPD-asthma phenotype</td>
<td>92.3</td>
<td>Recommendable criterion</td>
</tr>
<tr>
<td>No positive bronchodilator test (&gt;200 ml and &gt;12%) on treatment</td>
<td>86.6</td>
<td>Recommendable criterion</td>
</tr>
<tr>
<td>No decline after switch from high to low doses</td>
<td>80.7</td>
<td>Recommendable criterion</td>
</tr>
<tr>
<td>No eosinophilia in sputum</td>
<td>65.3</td>
<td>Recommendable criterion</td>
</tr>
<tr>
<td>No eosinophilia in peripheral blood</td>
<td>61.5</td>
<td>Recommendable criterion</td>
</tr>
<tr>
<td>Symptomatic stability determined by clinician’s impression</td>
<td>61.5</td>
<td>Recommendable criterion</td>
</tr>
<tr>
<td>Season of year</td>
<td>53.8</td>
<td>Recommendable criterion</td>
</tr>
<tr>
<td>Symptomatic stability determined by specific questionnaires (CAT®)</td>
<td>50</td>
<td>Recommendable criterion</td>
</tr>
<tr>
<td>Level of obstruction determined by FEV(_1)</td>
<td>46.1</td>
<td>Recommendable criterion</td>
</tr>
<tr>
<td>Nitric oxide in exhaled air</td>
<td>46.1</td>
<td>Recommendable criterion</td>
</tr>
</tbody>
</table>
general guidelines to help clinicians in the management of COPD patients, but they must be validated in prospective studies or randomized clinical trials.

The document has its limitations, including the fact that, inherent to the nature of this type of document, results can only be taken as expert opinions. The recommendations need to be backed up by clinical study to clarify the areas of uncertainty detected.

To conclude, this document has highlighted areas of consensus among experts on the use of ICS in the mixed COPD–asthma phenotype and in frequent exacerbators, on the unsuitability of ICS for improving lung function, and on the feasibility of IC withdrawal. Nevertheless, uncertainty regarding other aspects of this therapy could explain why the use of these drugs differs so widely among clinicians. If clinical practice is to improve, studies must be performed to examine and clarify these aspects.

Conflict of Interests

Bernardino Alcázar Navarrete has received fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Grupo Ferrer, GSK, Laboratorios Menarini, Novartis, Pfizer, Takeda for speaking engagements and/or scientific advice.

Ciro Casanova has received fees from Almirall, AstraZeneca, GlaxoSmithKline, Novartis for scientific advice and/or speaking engagements.

Marc Miravitlles has received fees from Almirall, AstraZeneca, Boehringer Ingelheim, Grupo Ferrer, GlaxoSmithKline, Grifols, Laboratorios Esteve, Pfizer, Novartis, Gebro Pharma and Takeda for scientific advice and/or speaking engagements.

Pilar de Lucas has received fees from Almirall, Boehringer Ingelheim, Novartis, Teva, Takeda for scientific advice and/or speaking engagements.

Juan Antonio Riesco has received fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Grupo Ferrer, GSK, Laboratorios Esteve, Laboratorios Menarini, Novartis, Pfizer, Takeda for giving speaking engagements and/or scientific advice.

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Appendix A. Working Group Members

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