



## Special article

## “Correct Use of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease”: A Consensus Document<sup>☆</sup>



Bernardino Alcázar Navarrete,<sup>a,\*</sup> Ciro Casanova,<sup>b</sup> Marc Miravittles,<sup>c</sup> Pilar de Lucas,<sup>d</sup> Juan Antonio Riesco,<sup>e</sup> José Miguel Rodríguez González-Moro<sup>d</sup>, on behalf of the Working Group “Consensus document on the appropriate use of inhaled corticosteroids in COPD”<sup>◇</sup>

<sup>a</sup> Neumología, Área integrada de gestión de Medicina, Hospital de Alta Resolución de Loja, APES Hospital de Poniente, Granada, Spain

<sup>b</sup> Servicio de Neumología, Unidad de Investigación, Hospital Universitario Nuestra Señora de la Candelaria, Tenerife, Spain

<sup>c</sup> Servicio de Neumología, Hospital Universitari Vall d'Hebron, Barcelona, Spain

<sup>d</sup> Servicio de Neumología, Hospital General Universitario Gregorio Marañón, Madrid, Spain

<sup>e</sup> Servicio de Neumología, Hospital San Pedro de Alcántara, Cáceres, Spain

## ARTICLE INFO

## Article history:

Received 25 July 2014

Accepted 6 November 2014

Available online 3 March 2015

## Keywords:

Chronic obstructive pulmonary disease

Inhaled corticosteroids

Guidelines

## ABSTRACT

**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.

© 2014 SEPAR. Published by Elsevier España, S.L.U. All rights reserved.

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

## RESUMEN

**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.

## Palabras clave:

Enfermedad pulmonar obstructiva crónica

Corticoides inhalados

Normativas

<sup>☆</sup> Please cite this article as: Alcázar Navarrete B, Casanova C, Miravittles M, de Lucas P, Riesco JA, Rodríguez González-Moro JM. Documento de consenso “Uso adecuado de los corticoides inhalados en la enfermedad pulmonar obstructiva crónica”. Arch Bronconeumol. 2015;51:193-198.

\* Corresponding author.

E-mail address: [balcazar@telefonica.net](mailto:balcazar@telefonica.net) (B. Alcázar Navarrete).

<sup>1</sup> The members of the Working Group “Consensus document on the appropriate use of inhaled corticosteroids in COPD” listed in [Appendix A](#).

**Método:** Se constituyó un grupo coordinador que realizó una revisión sistemática de la evidencia científica para proponer cuestiones que reflejaban áreas de incertidumbre relativas a la eficacia de los CI, los efectos adversos asociados a su empleo y los criterios para su retirada. Estas aseveraciones fueron sometidas a un panel de expertos mediante el método Delphi para comprobar el grado de consenso.

**Resultados:** Participaron en el panel 25 expertos, que alcanzaron el consenso en la indicación de CI en el fenotipo mixto EPOC-asma, en su empleo en el paciente con agudizaciones frecuentes y en no añadir CI a BDL para mejorar la función pulmonar del paciente con EPOC. En general, no hubo consenso en restringir el uso de CI motivado por sus efectos adversos. En cambio, el panel alcanzó el consenso en que la retirada del CI es factible pero debe hacerse de forma gradual y evaluando a corto plazo a los pacientes a los que se les retire.

**Conclusiones:** Existe consenso en la indicación de CI en pacientes con fenotipo mixto EPOC-asma y agudizador frecuente. Se deben considerar los posibles efectos adversos, pero no existe consenso en sí justifican restringir su indicación. También existe consenso en que la retirada de CI es factible.

© 2014 SEPAR. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

## Introduction

Chronic obstructive pulmonary disease (COPD) is highly prevalent. Data from Spain, based on the EPISCAN study,<sup>1</sup> suggest that it affects 10.2% of Spanish adults aged between 40 and 80 years. Worldwide, it is the third cause of death<sup>2</sup> and the fifth most burdensome disease in terms of disability-adjusted life years.<sup>3</sup>

Spanish COPD guidelines (GesEPOC) recommend the use of long-acting bronchodilators (LABD) as first line treatment, alone or in combination with other drug families (long-acting beta-agonists [LABA] and long-acting muscarinic antagonists [LAMA]), reserving the use of LABA+inhaled corticosteroids (IC) for frequent exacerbators with FEV1 <60% or mixed COPD-asthma phenotype, irrespective of severity.<sup>4</sup> This is in line with the GOLD 2011 strategy that positions IC+LABA as treatment for patients with severe COPD with frequent exacerbations.<sup>5</sup>

Numerous Spanish and international observational studies performed in different care settings have detected intensive use of ICs alone or combined with LABD in COPD patients. In Spain, several studies<sup>6–8</sup> have shown that over 60% of patients with mild COPD receive ICs (alone or in combination with LABDs), generally at high doses, irrespective of the care setting. This is in stark contrast with studies indicating that the mixed COPD-asthma phenotype is identified in less than 20% of patients,<sup>9</sup> and that only one third of patients are frequent exacerbators.<sup>10</sup>

In some cases, COPD patients receive combination IC+LABD without a clear indication. Others return to clinical stability after an initially correct indication, but continue with the treatment in the long-term. The beneficial effect of IC in stable COPD in terms of reducing exacerbations and improving other health outcomes is widely supported in the literature. However, it remains unclear whether the response is universal or if it only occurs in a subgroup with certain characteristics, known as IC responders. Moreover, these benefits are accompanied by potentially serious side effects derived from long-term use. In view of these considerations, a consensus document has been developed with the aim of determining the level of agreement in various areas where the use of IC+LABD may be unclear, in order to establish criteria for the appropriate use of IC in stable COPD.

## Material and Methods

This consensus document was drawn up by a group of professionals involved in the treatment and research of COPD with the aim of standardizing the use of IC in stable COPD. Members of the

consensus panel were selected on the basis of their research activities in COPD, their active participation in scientific forums, and their involvement in scientific societies dedicated to COPD care. The consensus process took place in 2 phases: in the first phase, a coordinator group was set up, consisting of the 6 authors of the document. The scientific evidence for the use of ICs in stable COPD was systematically reviewed. Three areas of interest were defined: (1) clinical benefits of the use of IC+LABD in stable COPD; (2) associated risks; and (3) evidence for IC withdrawal in stable COPD. In a second phase, after review of the evidence, areas of uncertainty in which expert opinion might converge in a consensus were detected for each area of interest. A total of 20 statements addressing these areas of uncertainty were drawn up and submitted to the panel for consensus. These questions were formulated exclusively by the members of the coordinator group, without the help of any external advisors, and submitted to the working group along with the complete review of the scientific evidence. Comments and suggestions for amending certain areas of the document or re-wording the questions for better understanding were noted. The expert group was given sufficient time to analyze the information provided and to make suggestions to the coordinator group before the voting process commenced.

The Delphi method was used to determine the level of agreement of the experts with regard to the statements on the use of IC in stable COPD. In this method, a questionnaire completed by a panel of experts is used to explore a route map for change. A summary of the expert opinions (in the form of quantitative evaluations and written comments) is provided as feedback to the same experts as part of the next round of the questionnaire.<sup>11</sup> This methodology has already been used on other occasions in the area of COPD.<sup>12,13</sup>

The consensus participants individually assessed their level of agreement with each statement on a 9-point Likert scale, ranging from 1 (completely disagree with the statement) to 9 (completely agree with the statement). These scores were divided into 3 final groups: agree (7–9 points), neither agree nor disagree (4–6 points) and disagree (1–3 points). Voting took place in the first round in a face-to-face meeting using an interactive voting system ([www.powervote.com](http://www.powervote.com)). Any questions that did not achieve consensus in the first round of voting were submitted to a second, final round and drafted, compiled and analyzed using online survey software ([www.surveymonkey.com](http://www.surveymonkey.com)). Consensus for each statement was established if at least 90% of the panel indicated their agreement with the statement in any of the 2 rounds, and the criterion for majority vote was met if at least 70% of the participants indicated agreement with the statement in any of the 2 voting rounds.

**Table 1**

Statements on the Efficacy of ICs in Stable COPD, With the Percentage of Agreement in the First and Second Rounds, and the Consensus Result.

	% Agreement in 1st round	% Agreement in 2nd round	Final results
In general, I would not add an IC to a LABA to improve a COPD patient's state of health	83	52	Indeterminate
In general, I would not add an IC to a LABA to improve a COPD patient's dyspnea	87.5	80	Majority
In general, I would not add an IC to a LABA to improve a COPD patient's lung function	76	92	Consensus
In general, I would not add an IC to a LABA to avoid lung function decline determined by FEV1	71	64	Indeterminate
In general, I would add an IC to a LABD to reduce the number of exacerbations in a COPD frequent exacerbator ( $\geq 2$ episodes/year) with FEV1 <50%	83.5	100	Consensus
In general, I would add an IC to a LABD in a COPD patient with a severe exacerbation	58	52	Indeterminate
In general, I would add an IC to a LABD in a COPD frequent exacerbator, irrespective of the level of severity determined by FEV1	54	92	Consensus
In general, I would add an IC to a LABD in a COPD patient with frequent infectious exacerbations	37.5	52	Indeterminate
In general, I would add an IC to a LABD in a patient with mixed COPD-asthma phenotype	100		Consensus

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**

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.

	% Agreement in 1st round	% Agreement in 2nd round	Final result
I would withdraw IC treatment in a patient on combined LABD+IC with community-acquired pneumonia	17	16	Indeterminate
I would change my approach when indicating IC+LABD in a COPD patient with a history of previous pulmonary tuberculosis	37.5	16	Indeterminate
I would change my approach when indicating IC+LABD in a COPD patient with a history of osteoporosis	20	20	Indeterminate
I would not change my approach when indicating IC+LABD in a COPD patient with a history of diabetes mellitus	72	72	Majority
I agree that treatment should begin with high dose IC+LABD	16	16	Indeterminate

### *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

**Table 3**

Statements on the Withdrawal of ICs in Stable COPD, With the Percentage of Agreement in the First and Second Rounds, and the Consensus Result.

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

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,<sup>14</sup> 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).<sup>15,16</sup>

The statement that an IC should not be added to a LABA to improve lung function determined by FEV1 in a COPD patient achieved consensus. This opinion is in line with several recent systematic reviews<sup>17,18</sup> showing that, while the use of ICs combined with LABAs improves FEV1, 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 FEV1 <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.<sup>4,5,19</sup> It is also

consistent with more recent studies showing that this combination can reduce exacerbations in patients with frequent exacerbations and FEV1 <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.<sup>20–22</sup>

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.<sup>23,24</sup> 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.<sup>25</sup>

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 4**

Criteria for IC Withdrawal in Stable COPD, With Level of Agreement and Final Recommendation of the Expert Group.

Criterion	% Agreement	Recommendation
No exacerbations in the previous 2 years	96.1	Recommendable criterion
No evidence of mixed COPD-asthma phenotype	92.3	Recommendable criterion
No positive bronchodilator test (>200 ml and >12%) on treatment	86.6	Recommendable criterion
No decline after switch from high to low doses	80.7	Recommendable criterion
No eosinophilia in sputum	65.3	
No eosinophilia in peripheral blood	61.5	
Symptomatic stability determined by clinician's impression	61.5	
Season of year	53.8	
Symptomatic stability determined by specific questionnaires (CAT®)	50	
Level of obstruction determined by FEV1	46.1	
Nitric oxide in exhaled air	46.1	



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 studies 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 Miravittles 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.

José Miguel Rodríguez González-Moro has received fees from Almirall, Boehringer Ingelheim, Chiesi, GSK, Laboratorios Menarini, Novartis, Pfizer for speaking engagements and/or scientific advice.

### Acknowledgements

This consensus study was made possible by an unrestricted grant from Novartis. The sponsor did not participate in any aspect of its design, conduct or drafting, their input being limited to the logistical organization. Participants did not receive any financial compensation for participation. The opinions expressed in this study are solely and exclusively those of the authors and reflect those of the consensus participants.

### Appendix A. Working Group Members

A. Fernández Villar (Complejo Hospitalario Universitario de Vigo, Pontevedra). A. Ruiz Sancho (Hospital de Alta Resolución de Loja, Granada). A. Huerta (Hospital Clínic, Barcelona). B. García Cosío (Hospital Universitario Son Espases, Palma de Mallorca). C. Esteban (Hospital Galdakao-Usasolo, Vizcaya). F. Ortega Ruiz (Hospitales Universitarios Virgen del Rocío, Seville). G. Peces Barba (Fundación Jiménez Díaz, Madrid). J.A. Quintano (Centro de Salud Lucena I, Córdoba). J.L. López Campos (Hospitales Universitarios Virgen del Rocío, Seville). J.L. Viejo Bañuelos (Burgos). J.J. Soler Cataluña (Hospital Universitario Arnau de Villanova, Valencia). J.P. de Torres (Clínica Universitaria de Navarra, Navarre). M. Román Rodríguez (Centro de Salud Son Pisa, Palma de Mallorca). M. Calle Rubio (Hospital Clínico San Carlos, Madrid). P. García Sidro

(Hospital de la Plana, Castellón). P. Sobradillo Ecenarro (Hospital Universitario Txagorritxu, Alava). P. J. Marcos (Complejo Hospitalario Universitario A Coruña, Coruña). P. Almagro Mena (Hospital Mutua de Terrasa, Barcelona). R. Agüero Balbín (Hospital Universitario Marqués de Valdecilla, Santander). R. Malo de Molina (Hospital Puerta de Hierro, Madrid).

### References

- Miravittles M, Soriano JB, García-Río F, Muñoz L, Duran-Tauleria E, Sánchez G, et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. *Thorax*. 2009;64:863–8.
- Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095–128.
- Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2197–223.
- Miravittles M, Soler-Cataluña JJ, Calle M, Molina J, Almagro P, Quintano JA, et al. Spanish guideline for COPD (GesEPOC). Update 2014. *Arch Bronconeumol*. 2014;50 Suppl. 1:1–16. S0300-2896(14)70070-5.
- Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2013;187:347–65.
- Izquierdo JL, Rodríguez Glez-Moro JM, de Lucas P, Martín Centeno A, Gobartt E. ¿Ha cambiado el manejo de la EPOC en España? Resultados de un estudio multicéntrico comunitario (VICE). *Rev Clin Esp*. 2008;208:18–25.
- Izquierdo JL, Martín A, de Lucas P, Rodríguez Glez-Moro JM, Almonacid C, Paravisini A. Misdiagnosis of patients receiving inhaled therapies in primary care. *Int J Chronic Obstruct Pulmon Dis*. 2010;5:241–9.
- Miravittles M, Brosa M, Velasco M, Crespo C, Gobartt E, González-Rojas N. An economic analysis of pharmacological treatment of COPD in Spain. *Respir Med*. 2009;103:714–21.
- Miravittles M, Soriano JB, Ancochea J, Muñoz L, Duran-Tauleria E, Sanchez G, et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. *Respir Med*. 2013;107:1053–60.
- Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363:1128–38.
- De Villiers M, de Villiers P, Athol K. The Delphi technique in health sciences education research. *Med Teach*. 2005;27:639–43.
- Soler-Cataluña JJ, Cosío B, Izquierdo JL, López-Campos JL, Marín JM, Agüero R, et al. Consensus document on the overlap phenotype COPD-asthma in COPD. *Arch Bronconeumol*. 2012;48:331–7.
- Krishnan JA, Lindenauer PK, Au DH, Carson SS, Lee TA, McBurnie MA, et al. COPD outcomes-based network for clinical effectiveness and research translation. Stakeholder priorities for comparative effectiveness research in chronic obstructive pulmonary disease: a workshop report. *Am J Respir Crit Care Med*. 2013;187:320–6.
- Disantostefano RL, Li H, Rubin DB, Stempel DA. Which patients with chronic obstructive pulmonary disease benefit from the addition of an inhaled corticosteroid to their bronchodilator? A cluster analysis. *BMJ Open*. 2013;3, pii:e001838.
- Kunisaki KM, Rice KL, Janoff EN, Rector TS, Niewoehner DE. Exhaled nitric oxide, systemic inflammation, and the spirometric response to inhaled fluticasone propionate in severe chronic obstructive pulmonary disease: a prospective study. *Thorax*. 2008;2:55–64.
- Leigh R, Pizzichini MM, Morris MM, Maltais F, Hargreave FE, Pizzichini E. Stable COPD: predicting benefit from high-dose inhaled corticosteroid treatment. *Eur Respir J*. 2006;27:964–71.
- Rodrigo GJ, Castro-Rodríguez JA, Plaza V. Safety and efficacy of combined long-acting beta-agonists and inhaled corticosteroids vs long-acting beta-agonists monotherapy for stable COPD: a systematic review. *Chest*. 2009;136:1029–38.
- Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta (2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012;9. CD006829.
- Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356:775–89.
- Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, Vestbo J, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med*. 2013;1:210–23.
- Agustí A, de Teresa L, De Backer W, Zvarich MT, Locantore N, Barnes N, et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. *Eur Respir J*. 2014;43:763–72.

22. Miravittles M. Arguments in favor of inhaled corticosteroids in COPD by phenotype instead of by severity. Arch Bronconeumol. 2011;47:271–3.
23. Nadeem NJ, Taylor S, Eldridge SM. Withdrawal of inhaled corticosteroids in individuals with COPD – a systematic review and comment on trial methodology. Respir Res. 2011;12:107.
24. Vogelmeier C, Bateman ED, Pallante J, Alagappan VKT, D'Andrea P, Chen H, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. Lancet Respir Med. 2013;1:51–60.
25. Magnussen H, Disse B, Rodriguez-Roisin R, Kirsten A, Watz H, Tetzlaff K, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N Engl J Med. 2014;371:1285–94.