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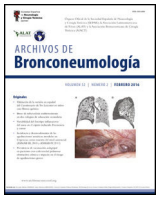

Editorial

Controlled Prescription of Triple Fixed-Dose Combination Therapy in Spain☆

La prescripción con visado de la triple terapia en combinación a dosis fija en España

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Triple therapy that combines a long-acting antimuscarinic (LAMA), a long-acting β_2 agonist (LABAS), and an inhaled corticosteroid (ICS) in a single inhalation device for the treatment of chronic obstructive pulmonary disease (COPD) has been available in Spain for few months. According to the summary of product characteristics, the therapeutic indication is "maintenance treatment in adult patients with moderate to severe COPD who are not adequately controlled with a combination of an ICS and a LABA or with a combination of a LABA and a LAMA".[1,2] In Spain, however, the Ministry of Health, Consumption and Social Welfare has established a particular limitation known as controlled prescription, that restricts the specific conditions for prescribing and dispensing this therapy in the National Health System. In this case, the controlled prescription terms specify that this therapy will be funded for patients who "are receiving treatment with a triple therapy consisting of ICS/LABA/LAMA, after having confirmed that they respond appropriately to the components administered separately, that is to say, patients in whom this treatment is stabilized and effective".[3] Leaving aside the significant discrepancy between the therapeutic indication and the funding requirements, we need to examine the wording and content of the controlled prescription terms, which are causing confusion.

In the first place, in contrast to the therapeutic indication, the controlled prescription text makes no express reference to COPD. Therefore, a patient with another chronic bronchial disease (e.g., asthma) could potentially meet the criteria of the controlled prescription. This could be interpreted as the approval of funding for an indication in diseases for which no clinical trials have been conducted with triple therapies.

Secondly, even if we stick to COPD treatment only, the indication and the funding requirements describe different patient profiles. Triple therapy was developed for patients who were not controlled with single or double therapy, and who required treatment escalation. Efficacy and safety data are available in this scenario that support the use of triple therapy. However, the controlled prescription appears to state (with the limitations in interpretation mentioned here) that combined therapy in a single device can be funded when the patient is already well controlled with triple therapy in separate devices. We have no data on what we might expect from this switch in the clinical setting. However, we do know that open or closed triple therapy is similarly effective in uncontrolled patients.[4,5] Therefore, the benefits expected from combining treatment in a single device would not apply so much to efficacy as to adherence,[6] fewer errors in the management of inhalers,[7] and potentially lower costs.[8] Therefore, if the 3 drugs are already being administered separately, it would make sense to combine them, but it would also make sense to use the combined therapy to escalate treatment if a patient needs triple therapy, adding the benefits in effectiveness to those achieved by better adherence, fewer critical errors, and reduced cost. Moreover, no data are available on the possible clinical impact of this switch in patients who are well-controlled with open triple therapy, but the variability of therapeutic responses in real life must be taken into account.[9]

Thirdly, the controlled prescription text states as a criterion that treatment must be "stabilized". However, what is meant by stabilized treatment is unclear from a both clinical and investigational point of view. In clinical terms, it is easy to apply this concept to a patient and we know what we mean when we speak of a stabilized patient, but not a stabilized treatment. The authors of the controlled prescription text might have meant a treatment that was maintained over time, but this time period is not specified. They may have meant that the patient should be stable, but stable means without changes. A patient could be considered stable if they remain symptomatic, with persistently poor control of symptoms. In either of the two interpretations, the text is confusing.

Fourthly, the controlled prescription text indicates that the treatment has to be effective. However, it does not define what it considers to be an effective inhaled treatment in a patient with severe COPD who needs 3 drugs for treatment. The effectiveness of

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a treatment can be evaluated from various clinical outcomes and from different cut-off points defining improvement. The definition of therapeutic efficacy or control in patients with severe COPD and, as such, a high disease impact is the subject of ongoing debate.[10]

Fifthly, the controlled prescription text does not specify that the separate components must be given at the same time. As it stands, a patient may respond to a LAMA and a LABA/ICS administered consecutively, but not necessarily concomitantly; and, having shown a good response to both separately, could be accepted for funding of triple therapy in a single device. Again, even if the components must be given at the same time, the length of time on open triple therapy before being able to switch to combined treatment in a single device is not specified, generating even more confusion.

Because of this confusion, each autonomous community has interpreted the requirements for controlled prescription differently, and as a result, patients do not have equal access to treatment.

In conclusion, there is currently considerable controversy regarding the criteria for funding triple therapy in a single inhalation device. The discrepancy between indication and funding and the confusing drafting of the controlled prescription text are creating unclear clinical situations with inequitable access, potentially impacting negatively on patients. The members of Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) believe that healthcare and clinical managers must work hand in hand to avoid situations of ambiguity, and we engage fully in collaborating to achieve standards that align with our socio-economic reality and which also make good clinical sense.

Conflict of Interests

JLLC has received honoraria in the last 3 years for speaking engagements, scientific consultancy, participation in clinical trials, and preparation of publications from (in alphabetical order): AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, Esteve, Ferrer, Gebro, GlaxoSmithKline, Grifols, Menarini, Novartis, Rovi and Teva. He is the current coordinator of the SEPAR COPD area.

GPC has received honoraria for participation in scientific conferences and scientific consultancy from GSK, Boehringer Ingelheim, Menarini, Esteve. He has received funding for scientific projects from GSK, Menarini, Esteve, Boehringer Ingelheim, and is the current Pulmonology Vice-chair of SEPAR.

CAJR has received honoraria in the last 3 years for speaking engagements, scientific consultancy, participation in clinical trials, and preparation of publications from (in alphabetical order): Gebro, GlaxoSmithKline, Menarini and Pfizer. He is the current Chair of SEPAR.

This document has been prepared by the authors on the basis of clinical studies and their own professional experience, without influence from the pharmaceutical industry.

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