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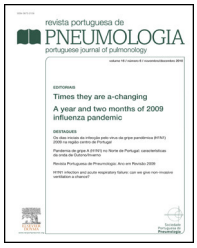

EDITORIAL

Inhaled steroids in COPD: Reasons for a debate

The indications (and contraindications) of treatment with inhaled corticosteroids (ICS) in patients with chronic obstructive pulmonary disease (COPD) are well established in the latest iteration of the Global Strategy for the Diagnosis, Management and Prevention of COPD (GOLD) document.[1] According to this document, ICS are *indicated* in COPD patients with severe or very severe airflow limitation (FEV1 < 50% of predicted) and/or frequent exacerbations (ECOPD) that are not adequately controlled by long-acting bronchodilators (Evidence A) because they reduce the risk of future episodes of ECOPD.[1] More recently, ICS have also been recommended for the treatment of the so-called Asthma-COPD overlap syndrome (ACOS).[2] On the contrary, ICS *should never be used* in mono-therapy (i.e., alone) in COPD patients[1] (an important difference vs. asthma[3]). Despite this, apparently straightforward situation, there is a lively debate on where ICS should be positioned in the treatment of COPD.[4] This Editorial briefly discusses what, in my opinion, are some of the main arguments that fuel this debate.

First, drug therapy in COPD was actually ''inherited'' from asthma and basically consisted in the use of long-acting β2 agonists (LABA) and ICS.[5] It is only recently that new long-acting bronchodilators have been developed specifically for the treatment of COPD (not asthma), as best exemplified by tiotropium (a long acting anti-muscarininc agent; LAMA).[6] Even more recently, new fixed combination of LABA-LAMA's have been also developed for COPD and can now be prescribed in many markets.[7,8] To my mind, the availability of these new therapeutic alternatives will inevitably force the academic community to carefully re-consider the position ICS within the therapeutic armamentarium of COPD.[4] For instance, the recent ILLUMINATE study[7] showed, not surprisingly, that lung function improvement was significantly better in patients who received a fixed combination of indacaterol (LABA) and glycopirronium (LAMA) than in those who received a fixed combination of salmeterol (LABA) and fluticasone propionate (ICS): two bronchodilators bronchodilate more than one!. Interestingly, authors did not find significant differences in the incidence of ''adverse events'' (including ECOPD).[7] This observation may indicate that a LABA-LAMA combination has a similar effect on ECOPD than a LABA-ICS combination and, remember, according to GOLD, ICS are indicated in COPD to reduce the risk of future exacerbations.[1] Yet, as it is often the case, the devil is in the details since: (1) this study lasted for 26 weeks only, probably a period of time that is too short to assess with certainty the effect of any treatment on the incidence of ECOPD; (2) the study included patients *without* a history of previous ECOPD,[7] when it is well established that the best predictor of future ECOPD is a previous history of ECOPD[9]; and, (3) patients who had a moderate-to-severe ECOPD were withdrawn from the study.[7]

Second, likely as a consequence of ICS being ''inherited'' from asthma, as discussed above, there is ICS over prescription in COPD,[4] particularly in patients classified in GOLD groups A or B, where ICS should not be theoretically prescribed.[1] Not surprisingly, therefore, there has been interest in studying the effect of ICS withdrawal in COPD. In this context, the WISDOM study published recently[10] concludes that in patients with severe COPD receiving tiotropium (LAMA) plus salmeterol (LABA) plus fluticasone propionate (ICS), the gradual discontinuation of the latter until complete suppression does not increase significantly the risk of moderate or severe ECOPD, albeit there was a significantly greater decline in lung function in those patients in whom ICS was withdrawn.[10] However, the devil is in the details again since: (1) an inclusion criterion in the WISDOM study was that patients must have had one or more ECOPD in the preceding year.[10] Given that 70% of the patients finally included in the study were already on ICS treatment during this period (plus LABA, LAMA or both),[10] this criteria implies *de facto* that patients who, while on ICS, had not had previous ECOPD were *excluded* from the study. In other words, the study excluded those patients who, theoretically, could benefit most from ICS and included those who, apparently, were not well controlled while on ICS. There should be no surprise then that ICS discontinuation in the latter did not have any major effect; and, (2) as acknowledged by the authors, there was a significant difference (43 ml in 10 months, $p < 0.001$) in the rate of FEV1 decline in favor of those patients who continued on ICS. Authors considered that this difference was not clinically relevant.[10] Personally I have to disagree with this interpretation, since the FEV1 of these patients at entry in the study was 900 ml only.[10] On the contrary, I

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believe that this indeed indicates that ICS treatment can contribute to reducing the excessive decline of lung function in COPD, as suggested by some previous reports.[11,12] In fact, other previous studies had also shown already that ICS withdrawal leads indeed to enhanced FEV1 decline.[13,14,22]

Third, and finally, treatment with ICS has been linked to an increased risk of pneumonia in COPD.[15] This also questions the positioning of ICS in the treatment of COPD. However, these are peculiar ''pneumonias'', since they do not increase the risk of mortality and, in some studies, they may even reduce it.[16] Further, a forgotten element in this debate is the optimal ICS dose to be used in COPD. Given that the dose-response curve of ICS is relatively flat (at least in terms of lung function changes),[17] it is possible that lower doses of ICS may have a more favorable efficacy/risk ratio in COPD.

In summary, despite the apparently straightforward recommendations of GOLD in relation to the positioning of ICS in the treatment of COPD discussed at the beginning of this Editorial,[1] certainly there are reasons for the debate. It is only through rigorous research that we will be able to answer these questions and to select those COPD patients who may benefit most from the use of ICS.[4,18] Having said that, however, it is also important to note that the framework of this debate can change radically if future research shows that ICS may have effects that go beyond ECOPD and/or lung function decline, including the chemoprevention of lung cancer,[19] one of the most frequent causes of death in COPD,[20] and/or the reduction of cardiovascular risk,[21] another very common cause of morbidity and mortality in these patients.[20] Stay tuned: the debate continues!

Conflicts of interest

I have received grant support and/or fees for speaking at conferences and/or participating in advisory boards related to COPD management from Almirall, AstraZeneca, Boheringer-Ingelheim, Chiesi, GSK, Kyorin, Menarini, MSD, Novartis, Takeda and TEVA.

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