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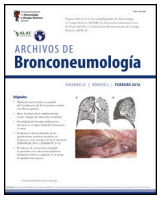

Discussion Letter

Multidisciplinary Management of Patients With Chronic Obstructive Pulmonary Disease and Cardiovascular Disease: Response to Additional Considerations

To the Director,

We thank Golpe and Figueira-Gonçalves for the interest and comments about our manuscript on multidisciplinary management of patients with chronic obstructive pulmonary disease and cardiovascular disease. We agree with them in highlighting the pro-arrhythmic effect derived from the use of some drugs used in the treatment of COPD, as well as in pointing out the precautions that must be taken into account when prescribing them and during the time how long his administration lasts.

Azithromycin has important inmuno-modulatory properties that make it effective in reducing COPD exacerbations. However, the benefits are not without penalty. In fact, the available evidence supports a small increased risk of cardiovascular death derived from long-term use related to QT interval prolongation. Most cardiovascular events occur in patients with concurrent risk factors, including preexisting cardiac disease and co-administration of QT prolonging drugs. Thus, physicians deciding whether to use this therapy must weigh each patient's individual risk of cardiovascular complications against the expected benefit, taking into account that patients with a history of cardiac disease, especially long QT syndrome or ventricular arrythmias, should probably do not receive chronic therapy with azithromycin. In any case, cost-effectiveness studies that consider the cost of adverse events as well as screening patients to avoid them, e.g., regular electrocardiogram to monitor QT Interval, are necessary.[1]

On the other hand, theopylline (dimethylxanthine) has been used for airway obstruction for about 100 years. Xanthines have bronchodilator and anti-inflammatory effects, but they may also cause adverse cardiac effects as a consequence of inhibition of adenosine receptors. According to current clinical practice guidelines, xantines are not considered as first-line drugs for COPD treatment. However, in patients who do not tolerate β-adrenergic agonists, they may still have a place, especially in younger adults without cardiac diseases.[2]

In relation to the treatment with triple therapy in patients with frequent exacerbations, its use in a single device manages to reduce the number of exacerbations, prevent hospital admissions and reduce mortality from all causes. However, it must be taken into account that the magnitude of the effect of ICS added to regular maintenance bronchodilator treatment is related to blood eosinophil count. A high blood eosinophil count (≥300 cells/μl) is an adjunctive parameter useful to define the subset of COPD subjects responsive to ICS, and can be used to identify patients with the greatest likelihood of benefit with ICS treatment. On the other hand, combinations containing ICS have little or no effect if blood eosinophil count < 100 cells/μl. Therefore, this threshold value can be used to identify patients with a low likelihood of treatment benefit with ICS and greater complications associated with its use.[3] However, the thresholds of ≥300 cells/μl and <100 cells/μl have been suggested to predict different probabilities of treatment benefit, but they should be considered as estimates, rather than precise cut-off values. Furthermore, recent guidelines are more progressive in the use of triple therapy, removing the eosinophil blood count threshold when patients with frequent exacerbations are not well controlled with LAMA/LABA therapies in order to prevent hospital admissions and reduce all-cause mortality,[4] although this aspect is controversial and there is no clear evidence to support it.

Despite everything, it is important to remember that the use of ICSs in COPD patients is not free from adverse events. The highest risk corresponded to local disorders, such as oral candidiasis and dysphonia, followed by infectious complications such as pneumonia, and diabetes-related outcomes, although with lower frequency. However, the risks of osteoporosis, bone fractures and eye disorders are les clear. For most of these complications a dose–response relationship has been described, indicating that lower doses of ICS should be used in patients with COPD whenever posible. It should be noted that, among the factors associated with a greater risk of developing pneumonia, it has been described, precisely, a low blood eosinophils count.[5] In this way, both, the clinical assessment and the blood eosinophil count, used as a biomarker, must be taken into account, today, when making decisions regarding ICS use in COPD patients.

Conflict of interests

J. de Miguel-Díez has received grants and honoraria from AstraZeneca, BIAL, Boehringer, Chiesi, FAES, Gebro, GSK, Janssen, Menarini, Novartis, Sanofi, Roche, Teva, Pfizer and Zambón.

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