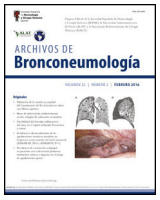
Archivos de Bronconeumología 58 (2022) 593–594

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Editorial

Is it Time to Readjust the Doses of Inhaled Corticosteroids in COPD?

The old discussion by the end of the last century about the use of inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD) generated a lot of ink and dialectical confrontations – sometimes heated – between the defenders of the role of ICS in COPD, who based their arguments on the effect on the prevention of exacerbations (and the much discussed p value = 0.052 of the TORCH[1] study, – do you remember that?), and the ardent defenders of the FLAME[2] study, which made ICS the enemy to beat, partly supported by clear signs of an increased risk of pneumonia associated with this treatment. The scientific evidence generated in recent years has been making both sides happy, while front-line clinicians have seen with astonishment the futility of the arguments being put forward on both fronts, far removed from clinical reality. This was well-reflected in the clinical audit carried out by the EPOC-consul study,[3] which showed that 60% of patients with COPD in Spain received treatment with ICS. The incorporation of eosinophils as a biomarker of response to ICS treatment also helped to satisfy both sides, identifying a clear profile of responders that the GesEPOC[4,5] guidelines previously classified as mixed phenotype or ACO (Asthma COPD overlap)[6] and now see as an eosinophilic exacerbator. International guidelines such as GOLD[7] have also opted to direct treatment with ICS to patients with higher peripheral blood eosinophil values in a first assessment, although they also leave its use open in patients with repeated exacerbations and peripheral blood eosinophil counts above 100 cells/μL.

Eventually, all these discussions were settled after the publication of studies with fixed triple therapy in COPD (TRIBUTE,[8] IMPACT[9] and ETHOS[10]) that consolidated the previous evidence on the efficacy of ICS in preventing exacerbations in exacerbator patients with FEV1 < 50%.

Even after this point has been accepted, however, many clinicians who often follow severe COPD patients with frequent exacerbations caused by potentially pathogenic bacteria (PPB) (frequently *Pseudomonas aeruginosa* in the most severe cases)[11] still wonder how treatment with ICS can influence the long-term outcome of these patients, considering this treatment's immunosuppressive properties, and even more pertinently, the ICS doses recommended by the guidelines, which are medium or high doses (1000 μg of fluticasone propionate or equivalent). Not surprisingly, there is scientific evidence to show that ICS can modify the lung microbiome,[12] selecting more aggressive strains such as *Pseudomonas aeruginosa*. However, what if we are using doses that are too high in these patients, who also receive frequent cycles of antibiotics and oral corticosteroids, due to their exacerbator profile? The use of ICS in patients with blood eosinophil counts < 100 cells/μL undoubtedly increases the risk of infection and worsens the prognosis, as shown by the studies published by Martínez-Garcia et al.[13] However, it is also possible that eosinophils are not such a good biomarker in the most severely ill patients, who are often underrepresented in clinical trials and only provide us with information about the risk of side effects in patients with repeated severely decreased eosinophil counts. Eosinopenia in COPD appears to be a mortality risk marker in exacerbations[14] (also in SARS-CoV2[15] infection), leaving aside the use of ICs, but the efficacy of ICs in preventing exacerbations has been demonstrated, regardless of the number of eosinophils. Are the currently approved doses of ICS ideal for the most severe COPD patients who have frequent exacerbations with an infective profile? Should we not use lower doses[16] if it is shown that these continue to prevent exacerbations? Anzueto et al.[17] showed that half the approved dose of fluticasone propionate (250 μg every 12 h) was equally effective in reducing exacerbations. Meanwhile, research carried out by our group[18] in a population with severe COPD has shown that high-dose ICS are associated with a higher risk of *Pseudomonas aeruginosa* infection and higher mortality – an effect not observed at low doses. In other words, the effect on the risk of infection and on mortality is probably not associated with the use of ICS by itself, but rather with the use of high doses of this treatment. Moreover, this effect is independent of the number of peripheral eosinophil counts. These findings have recently been reproduced in a Danish cohort of 21,000 COPD patients, showing a dose-dependent association between the use of ICS and the risk of *Pseudomonas aeruginosa* infection.[19]

To modify the recommendations for IC doses, especially in patients with more severe COPD, we need scientific evidence to show that in this profile the use of low-dose ICs is more effective than not using ICS at all. Recently, at the COPD-Integrated Research Program meeting in SEPAR, the "*Study on the Doses of Inhaled Corticosteroids in ePOc*" (EDIPO) was presented to test the hypothesis that low doses of ICS (corresponding to 100 μg every 12 h of fluticasone propionate or equivalent) are as effective in reducing exacerbations as the currently used high doses, but with a lower risk of BPP infections. If the proposed hypothesis is proven and the ICS dose recommendations modified, many questions would thus be cleared up with respect to the management of those more severe COPD patients who frequently overwhelm our pulmonology clinics.

References

1. 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.

https://doi.org/10.1016/j.arbres.2022.01.014

2. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al., FLAME Investigators. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. N Engl J Med. 2016;374:2222–34.
3. Calle Rubio M, Alcázar Navarrete B, Soriano JB, Soler-Cataluña JJ, Rodríguez González-Moro JM, Fuentes Ferrer ME, et al. Clinical audit of COPD in outpatient respiratory clinics in Spain: the EPOCONSUL study. Int J COPD. 2017;12:417–26.
4. Miravitlles M, Calle M, Molina J, Almagro P, Gómez JT, Trigueros JA, et al. Spanish COPD Guidelines (GesEPOC) 2021: updated Pharmacological treatment of stable COPD. Arch Bronconeumol. 2022;58:69–81.
5. Miravitlles M, Calle M, Soler-Cataluña JJ. GesEPOC 2021: one more step towards personalized treatment of COPD. Arch Bronconeumol. 2021;57:9–10.
6. Soler-Cataluña JJ, Novella L, Soler C, Nieto ML, Esteban V, Sánchez-Toril F, et al. Clinical characteristics and risk of exacerbations associated with different diagnostic criteria of asthma-COPD overlap. Arch Bronconeumol. 2020;56:282–90.
7. Halpin DMG, Criner GJ, Papi A, Singh D, Anzueto A, Martinez FJ, et al. Global initiative for the diagnosis, management, and prevention of chronic obstructive lung disease. The 2020 GOLD science committee report on COVID-19 and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2021;203:24–36.
8. Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet (Lond, Engl). 2018;391:1076–84.
9. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al., IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med. 2018;378:1671–80.
10. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, et al., ETHOS Investigators. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. N Engl J Med. 2020;383:35–48.
11. de la Rosa Carrillo D, López-Campos JL, Alcázar Navarrete B, Calle Rubio M, Cantón Moreno R, Máiz Carro L, et al. Comité Asesor del Documento; Comité Asesor del Documento de consenso sobre el diagnóstico y tratamiento de la infección bronquial crónica en la enfermedad pulmonar obstructiva crónica. Consensus document on the diagnosis and treatment of chronic bronchial infection in chronic obstructive pulmonary disease. Arch Bronconeumol (Engl Ed). 2020;56:651–64.
12. Leitao Filho FS, Takiguchi H, Akata K, Ra SW, Moon JY, Kim HK, et al. Effects of Inhaled Corticosteroid/Long-Acting β2-Agonist Combination on the Airway Microbiome of Patients with Chronic Obstructive Pulmonary Disease: A Randomized Controlled Clinical Trial (DISARM). Am J Respir Crit Care Med. 2021 Nov 15;204:1143-1152.
13. Martinez-Garcia MA, Faner R, Oscullo G, de la Rosa D, Soler-Cataluña JJ, Ballester M, et al. Inhaled steroids, circulating eosinophils, chronic airway infection, and pneumonia risk in chronic obstructive pulmonary disease. a network analysis. Am J Respir Crit Care Med. 2020;201:1078–85.
14. Mao Y, Qian Y, Sun X, Li N, Huang H. Eosinopenia predicting long-term mortality in hospitalized acute exacerbation of COPD patients with community-acquired pneumonia – a retrospective analysis. Int J Chron Obstruct Pulmon Dis. 2021;16:3551–9.
15. Cosio BG, Shafiek H, Toledo-Pons N, Iglesias A, Barcelo M, Represas-Represas C, et al. Characterization of COPD admissions during the first COVID-19 outbreak. Int J Chron Obstruct Pulmon Dis. 2021;16:1549–54.
16. Cosio BG, Izquierdo JL, Cosio BG. The dose of inhaled corticosteroids in patients with COPD: when less is better. Int J Chron Obstruct Pulmon Dis. 2018.
17. Anzueto A, Ferguson GT, Feldman G, Chinsky K, Seibert A, Emmett A, et al. Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. COPD. 2009;6:320–9, http://dx.doi.org/10.1080/15412550903140881.
18. Shafiek H, Verdú J, Iglesias A, Ramon-Clar L, Toledo-Pons N, Lopez-Causape C, et al. Inhaled corticosteroid dose is associated with *Pseudomonas aeruginosa* infection in severe COPD. BMJ open Respir Res. 2021;8:e001067. C8496398.
19. Eklöf J, Ingebrigtsen TS, Sørensen R, Saeed MI, Alispahic IA, Sivapalan P, et al. Use of inhaled corticosteroids and risk of acquiring Pseudomonas aeruginosa in patients with chronic obstructive pulmonary disease. Thorax. 2021, thoraxjnl-2021-217160.

Borja G. Cosío [a,*], Hanaa Shafiek [b], Miguel Ángel Martínez-García [c]
[a] *Servicio de Neumología, Hospital Universitario Son Espases-IdISBa-CIBERES, Spain*
[b] *Chest Diseases Department, Faculty of Medicine, Alexandria University – Alexandria, Egypt*
[c] *Servicio de Neumología, Hospital Universitario La Fé, Valencia, Spain*

Corresponding author.
E-mail address: borja.cosio@ssib.es (B.G. Cosío).