Inhaled corticosteroids and pneumonia mortality in COPD patients

To the Editor:

In a recent article, Suissa [1] proposes several alternative hypotheses to explain the paradoxical effect of inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD) patients, whereby these drugs can increase the risk of pneumonia and simultaneously reduce pneumonia mortality. In our opinion, the conclusion of the article, that pneumonia mortality is increased in COPD patients treated with ICS, both in observational and in randomised clinical trials (RCTs), is not supported by data and cannot be considered confirmed. Basically, the author maintains that this paradox can be explained by the small number of events in randomised clinical trials (RCTs) and selection bias in observational studies [1].

First, pneumonia risk is increased in patients with COPD, and chronic treatment with ICS further increases this risk [2, 3]. However, this higher incidence of pneumonia is not uniform in different studies, and in recent RCTs conducted in a large number of patients the incidence of pneumonia was not increased in patients randomised to ICS treatment [4–6]. This suggests that other factors, such as the specific drug, dose and population studied, may affect this risk.

Suissa [1] suggests that ICS-treated patients may develop pneumonia for the same reasons as the rest of COPD patients, and additionally due to factors directly attributable to ICS. Two different concepts used by the author should be clarified: 1) pneumonia mortality (pneumonia deaths/total number of patients), and 2) case fatality (pneumonia deaths/number of patients with pneumonia). Following the same example used in the article, if the risk of pneumonia in ICS users is 2, and the prognosis of severe cases of pneumonia (case fatality) is similar for ICS and non-ICS users, global mortality for pneumonia in ICS users should be 2. Conversely, if pneumonia mortality is similar, the prognosis of severe cases of pneumonia should be 0.5. In our opinion, this option is more realistic since in the meta-analysis conducted by Festic *et al.* [3] case fatality in observational studies was lower in ICS users (RR 0.7, 95% CI 0.59–0.88).

Secondly, Suissa [1] proposes that the lower mortality for pneumonia observed in these studies can be explained by selection bias. The argument is that this lower mortality in ICS patients may be related to fewer comorbidities or having less severe COPD, among other factors. However, observational studies statistically adjust for many of these possible confounders, and we cannot find any plausible reason to explain why patients not treated with ICS should have more comorbidities or more severe COPD than ICS-treated patients [7].

To avoid this bias Suissa [1] analysed a cohort study defined by ICS exposure at inclusion. In this study, performed between 1998 and 2003, pneumonia mortality was increased in ICS patients. However, global mortality was lower with ICS use, which can lead to a bias (only living patients can die of pneumonia). In subsequent publications, S. Suissa and co-workers confirm that ICS patients had an increased risk of severe pneumonias, but regrettably, the authors did not explore the mortality data in these studies [8, 9].

Finally, the meta-analysis of RCTs referenced in the article showed an increase in pneumonia mortality among patients treated with ICS, though this relationship did not reach statistical significance (RR 1.50, 95% CI 0.85–2.67), and the authors concluded that the risk of pneumonia mortality was not increased in ICS users [3]. Suissa [1] suggests that the reason is the limited number of events. This may be a factor, but the total number of patients included in this meta-analysis is considerable (12 958 patients). Of note, since the publication of this meta-analysis, at least 10 RCTs containing 40 424 COPD patients randomised to ICS treatment have been published (table 1). Of these, in seven (24 811 patients) non-fatal pneumonia

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Chronic use of ICS increases the risk of pneumonia in COPD patients, although this risk is not homogenous. This study confirms that the risk of pneumonia-related mortality in randomised clinical trials is not increased in patients treated with ICS. http://bit.ly/2Zod6us

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TABLE 1 Pneumonia mortality in randomised clinical trials

Studies	Drug	Patients			Pneumonia mortality	
		Total	ICS	Non-ICS	ICS	Non-ICS
Included in meta-analysis [3]						
Calverley, 2011 (INSPIRE) [10]	Fluticasone propionate	1323	658	665	3	0
Crim, 2009 (TORCH) [11]	Fluticasone propionate	6112	3067	3045	21	16
Dransfield, 2013 [12]	Fluticasone furoate	3255	2437	818	8	0
Kardos, 2007 [13]	Fluticasone propionate	792	408	384	1	1
SCO40041 [14]	Fluticasone propionate	186	92	94	2	1
Sharafkhaneh, 2012 [15]	Budesonide	1218	815	403	1	0
Total		12886				
Not included in meta-analysis						
Ferguson, 2017 (RISE) [16]	Budesonide	1219	606	613	0	0
Vestbo, 2016 (SUMMIT) [4]	Fluticasone furoate	16485	8256	8229	0	0
Papi, 2018 (TRIBUTE) [5]	Beclometasone	1532	764	768	0	0
Vestbo, 2017 (TRINITY) [17]	Beclometasone	2691	1616	1705	0	0
Lipson, 2018 (IMPACT) [18]	Fluticasone furoate	10355	8285	2070	19	9
Ferguson, 2018 (KRONOS) [6]	Budesonide	1896	1271	625	1	0
Siler, 2017 [19]	Fluticasone furoate	1620	806	814	0	0
Wedzicha, 2016 (FLAME) [20]	Fluticasone propionate	3362	1682	1680	2	6
Zongh, 2015 (LANTERN) [21]	Fluticasone propionate	741	369	372	0	0
Vogelmeier, 2013 (ILLUMINATE) [22]	Fluticasone propionate	523	264	259	0	0
Total		40424	31396	22544	58	33

cases were reported. We performed a joint analysis of the RCTs included in the meta-analysis of Festic *et al.* [3] and those published subsequently with a total of 53940 patients (31396 ICS and 22544 non-ICS). In this analysis, mortality from pneumonia was 58/31396 for ICS users and 33/22544 for non-ICS. (RR 0.97, 95% CI 0.58–1.60; p=0.89, I^2=7.8%). We believe that these data reinforce the notion that pneumonia-related deaths are very infrequent in RCTs and, given the number of patients included, the clinical relevance of ICS in pneumonia mortality is doubtful.

Certainly, pneumonia is an undesirable event, but the increased risk of pneumonia in COPD patients should be counter-balanced by a decrease in exacerbations, especially the most severe that require hospitalisation, and that lead to an increase in mortality, as Suissa *et al.* [23] have previously demonstrated.

Therefore, we believe that the conclusion stated by Suissa [1] that: "the evidence is now clear that ICS use is associated with a higher incidence of pneumonia and of pneumonia-related mortality", is debatable, given available data. The use of ICS should be in accordance with current recommendations, and clinicians must balance the pneumonia risk with the reduction in both severe exacerbations and the mortality.

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From the authors:

I thank P. Almagro and co-workers for their letter, which provides updated data regarding the association between inhaled corticosteroids (ICS) and pneumonia mortality in chronic obstructive pulmonary disease (COPD). It confirms the shortage of, and need for, rigorous studies on this question. My article, on the other hand, was focusing on a methodological, causal inference explanation for the paradoxical phenomenon of

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observational studies reporting that ICS use increases the incidence of pneumonia in contrast with other observational studies reporting that ICS use prior to a pneumonia event decreases mortality [1].

Nevertheless, their conclusion that in using ICS in COPD "clinicians must balance the pneumonia risk with the reduction in both severe exacerbations and the mortality" is not founded on the evidence available to date. This conclusion implies that while ICS increase the risk of pneumonia, they are also effective at reducing the incidence of both severe exacerbations and mortality. The latter is not supported by the totality of evidence. Indeed, a network meta-analysis of 99 randomised controlled trials shows that ICS do not reduce the incidence of severe exacerbations in COPD, on the contrary they appear to increase it, when compared with mono or dual bronchodilators [2]. This meta-analysis also corroborates the increased risk of pneumonia with ICS [2]. With respect to mortality, only observational studies reported a reduction in all-cause death with ICS [3, 4]. However, these studies were shown to be seriously affected by immortal time bias, which tends to exaggerate a drug's beneficial effect [5, 6]. Observational studies that were designed to avoid this bias showed no reduction in mortality [7]. To date, no randomised trial has shown that ICS are associated with a reduction in mortality [2, 8].

Therefore, the evidence-based balance that clinicians should be concerned with when prescribing ICS *versus* long-acting bronchodilators in patients with COPD is between the risk of pneumonia and perhaps a reduction of mild and moderate exacerbations, but certainly not the severe ones or mortality, as suggested by P. Almagro and co-workers.

The more recent observational studies conducted in real-world clinical practice settings suggest that ICS may be effective at reducing moderate exacerbations only in the subset of patients with significant eosinophilia or frequent exacerbators [9, 10]. Consequently, with the established risk of pneumonia with ICS, this therapy should only be used sparingly in the subset of COPD patients for whom the benefit may outweigh the risk, such as patients with asthma, frequent exacerbators and those with significant eosinophilia [11, 12]. More research is needed to better identify such markers for a more accurate precision medicine approach to the treatment of COPD patients [13].

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