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Journal club

Does inhaled corticosteroid use affect the risk of COVID-19-related death?

Commentary on:
Schultze A, *et al*. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform. *Lancet Respir Med* 2020; 8: 1106–1120.

Context

Inhaled corticosteroid (ICS) is extensively used in the management of asthma [1], and used in a large fraction of COPD patients [2–4]. Clinical reports from the first months of Coronavirus disease 2019 (COVID-19) have shown a lower incidence of COVID-19 in patients with COPD and asthma compared with the general population [5, 6]. These differences could be explained by the treatment received, but also by differences in behaviour.

This reduced incidence is conflicting with the fact that patients with COPD have worse outcomes when infected, as measured on the risk of hospitalisation, severity and mortality [6–8]. The same is true for asthma patients, but the effect size seems smaller [7, 9].

ICS is often regarded as an immunosuppressive drug and it can be hypothesised that this could be harmful in relation to COVID-19 [10]. ICS use in COPD is associated with increased risk of pneumonia [11] and ICS usage in both asthma and COPD is associated with increased risk of upper respiratory tract infections [12]. Conversely, *in vitro* studies have shown that ciclesonide blocks Middle East respiratory syndrome coronavirus (MERS-CoV) replication [13] and that glycopyrronium and formoterol decreased viral titers and cytokine production [14]. Furthermore, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial showed that treatment with the systemic corticosteroid dexamethasone reduced mortality in hospitalised patients who needed supplementary oxygen [15]. However, dexamethasone was only beneficial in severe cases, so it is not obvious if this translates into prophylactic effects of ICS [16].

A systematic review prior to the study discussed here found that there was no evidence of either harm or benefit of ICS in COVID-19 patients [10]. This leaves the effects of ICS on COVID-19 unclear.

Methods

This study [17] is an observational cohort study in which 147 557 persons with COPD and 818 490 patients with asthma were followed from March 1, 2020 (index date), until May 6, 2020. Individuals were eligible for the COPD cohort if they were ≥35 years, had a diagnosis of COPD, were a current or former smoker and were prescribed an ICS and a long-acting β-agonist (LABA) with or without a long-acting muscarinic agonist (LAMA) within 4 months prior to the index date. Patients were excluded when having other chronic

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ICS does not seem to protect against COVID-19-related mortality, but more data is needed to determine whether it is harmful. Due to its known and important benefits ICS should be prescribed as usual for both asthma and COPD. https://bit.ly/3pWVimX

respiratory comorbidities if they were diagnosed with asthma within 3 years or had received prescriptions indicative of asthma.

Eligibility for the asthma cohort required age ≥18 years, diagnosis with asthma within 3 years of the index date and a prescription with ICS or short acting β-agonist (SABA) within 4 months before the index date. Patients were excluded if they had other chronic respiratory comorbidities, if they were diagnosed with COPD within 3 years or had received prescriptions indicative of COPD.

In the COPD group, patients receiving at least one ICS prescription within 4 months prior to the index date either in combination with LABA or LAMA–LABA were compared with patients receiving LAMA-LABA and no ICS. In the asthma cohort, patients receiving ICS within 4 months prior to the index date (grouped as high dose and medium or low dose) were compared to patients receiving SABA only.

The primary outcome was death from COVID-19, which was analysed using proportional hazards regression adjusted for relevant confounders.

Main results

In the COPD population, 29.2% had received a prescription for LAMA–LABA, while 70.8% had received prescriptions for ICS in combination with LABA or LAMA–LABA. Demographics and comorbidities were similar between the two groups except for asthma which was more common in the ICS-treated group. Patients in the ICS group were also more likely to have had an acute exacerbation within the last year (26.0% compared with 19.7%).

In the asthma population, the mean age was approximately 50 years with a trend towards increasing age towards the group receiving high ICS doses. Individuals receiving ICS were also more likely to be women and generally with more comorbidities. There was also an association between ICS usage and exacerbations. The percentage of patients with exacerbations within the past year ranged from 14.0% in the SABA-only group to 36.3% in the high-dose ICS group.

In the COPD population, an unadjusted model showed that ICS prescription was associated with an increased risk of death (hazard ratio (HR) 1.53, 95% CI 1.22–1.93). Adjusting for age, sex and comorbidities did not alter this signal (HR 1.39, 95% CI 1.10–1.76).

In the asthma population a single variable model showed a similar increase in risk of death (HR 1.36, 95% CI 1.01–1.84) for low- or medium-dose and high-dose ICS (HR 2.30, 95% CI 1.64–3.23). This excess risk was not evident after confounder adjustment for age, sex and comorbidities in the low or medium dose ICS group (HR 1.02, 95% CI 0.76–1.37); however, there still seemed to be an excess risk in the high-dose ICS group (HR 1.55 95% CI 1.10–2.18).

Commentary

This is the first paper to inform on the association between ICS usage and risk of death in COVID-patients and there is currently little other data on the subject. The study included a large number of patients and found an increase in risk of COVID-19 associated death in both populations using an adjusted proportional hazards model as well as a model based on inverse probability of treatment weighting. There is a reasonable biological explanation as to why this could be the case based on the immunosuppressive effects of ICS. The signal is also consistent between the asthma and the COPD group and it seems to exhibit a dose dependence in the asthma group. In the RECOVERY trial, a tendency to an increased risk of death was found in the patients at the mildest stage of disease when treated with systemic corticosteroids [15]. This could indicate that corticosteroids tend to harm in mild COVID-19, though the adjusted absolute risk difference in this study was very small (0.09% and 0.03% for COPD and asthma, respectively) which would have limited clinical significance, if it were to be true.

Furthermore, it is important to keep in mind that the treatment and control groups in both cohorts differ on key parameters at baseline indicating that between-group analyses might be confounded by baseline differences. Even when adjusting for suspected confounders, it is possible that the observed differences are still due to residual confounding from unadjusted confounders.

In the COPD cohort, 19.7% of individuals in the control group had at least one acute exacerbation within the last year, while the same was true 26.0% of the ICS group. Acute exacerbations are a main driver of poor outcomes in COPD patients and a strong indicator of disease severity. This indicates that ICS is given to patients with higher risk of exacerbation, which is recommended by GOLD guidelines [2]. Even though the authors of the study adjusted for exacerbation frequency and comorbidities, confounding by indication cannot be ruled out. In both asthma and COPD, ICS is generally prescribed for more severe disease. The authors were not able to adjust for long-term home oxygen use, though this is an important risk factor for COVID-19 mortality. Patients with home oxygen are likely to receive triple therapy. In their sensitivity analysis a decreased risk of death in patients receiving ICS–LABA compared with ICS–LAMA–LABA was found. The two therapies have similar ICS contents so ICS cannot explain this difference.

The asthma group also had noticeable baseline differences. Patients receiving higher doses of ICS were older, had more asthma exacerbations, and were more likely to have most of the comorbidities included in the study. Adjusting for this lowered the relative risk of death in both groups, and it became statistically insignificant in the low- or

medium-dose ICS group, but the signal was still present in the high-risk group. This could be explained either entirely by confounding, or it could be possible that only the highest ICS doses cause enough harm for it to be measurable. Also, worth considering is that asthma is underrepresented in COVID-19 hospitalisations globally, conflicting with the notion that ICS should be harmful, though this could also be explained by differences in patient behaviour.

Implications for practice

There are still sparse data available to determine the effect of ICS on COVID-19 mortality. This study provides evidence that ICS provides no protection from COVID-19 but gives no answers as to whether ICS is detrimental to COVID-19-related mortality. The biological plausibility, the strength of the signal and the consistency in both asthma and COPD point in favour of an interpretation of ICS being harmful. On the other hand, the baseline differences in the groups, the increased risk of non-COVID death in COPD patients receiving ICS and the potential unadjusted confounders point toward the observed differences being caused by confounding. ICS is an important drug in the management of both asthma and COPD. When indicated it reduces symptoms, improves health status and prevents future exacerbations. The latter is especially important with the ongoing pandemic, as the risk of hospital-acquired COVID-19 infection must be considered. More research is needed to discern the interaction between COVID-19 and ICS but, as of now, the known benefits outweigh the risks. For this reason, prescription of ICS should continue according to current guidelines. Nor should these results discourage withdrawal from ICS when indicated.

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Conflict of interest

A. Jordan has nothing to disclose. P. Sivapalan reports personal fees from Boehringer Ingelheim, outside the submitted work. J-U. Jensen has nothing to disclose.

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