Inhaled corticosteroids and COVID-19 outcomes in asthma: the Israeli experience

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To the Editor:

Inhaled corticosteroids (ICS), alone or in combination with bronchodilators, are widely used in asthma [1]. ICS have potential immunosuppressive effects that may promote viral replication, delayed viral clearance and increased risks of secondary infections [2, 3]. Furthermore, ICS use in asthma is associated with an increased risk of upper respiratory tract infections [2, 3]. Therefore, in the face of the current coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, concerns have been raised whether the use of ICS in asthmatic patients increases the risk of SARS CoV-2 infection and affects COVID-19 severity and mortality.

In the current study, we examined two objectives: 1) the association between ICS use and SARS-CoV-2 infection in asthmatic patients, using a test negative case–control study approach; and 2) the association between ICS use in asthmatic patients with PCR positivity for SARS-CoV-2 and COVID-19 severity and mortality, using a retrospective cohort study approach.

The study was approved by the Clalit Health Services (CHS) institutional review board and was exempt from the requirement for informed consent.

We used the computerised database of CHS to retrospectively identify all ⩾18-year-olds with an asthma diagnosis (International Classification of Diseases, ninth revision: 493.xx) who had seen at least twice by a pulmonologist in the past 5 years and underwent PCR testing for SARS-CoV-2 between 1 March 2020 and 17 December 2020. All identified patients who underwent PCR testing for SARS-CoV-2 served to assess the association between ICS use and SARS-CoV-2 infection, using a test negative case–control study approach. In this approach, positive PCR patients constituted the cases and negative PCR patients constituted the control group. Asthmatic patients with positive PCR for SARS-CoV-2 served to assess the association between ICS use and moderate–severe COVID-19 and with composite of moderate–severe COVID-19 and 90-days all-cause mortality, using a retrospective cohort study approach. COVID-19 severity was defined according to the Israeli Ministry of Health's guidelines, which are in accordance with the World Health Organization definitions [4].

ICS use was determined using the CHS pharmacy records using the Anatomical Therapeutic Chemical classification codes. Based on the timing of ICS prescriptions filled in the previous year, patients were classified into three categories: none *versus* recent (⩽90 days) *versus* former (90–365 days).

Logistic regression models were used to examine the association between ICS and PCR positivity, and Cox proportional hazard regression models were used to assess the association between ICS use and COVID-19 severity. Multivariable models were adjusted for age, sex, ethnicity, diabetes, hypertension, ischaemic heart disease, obesity, hospitalisation in the prior year and systemic corticosteroid use.

A total of 10 242 asthmatics (age ⩾18 years) underwent PCR testing for SARS-CoV-2 between 1 March 2020 and 17 December 2020. Of them, 6688 (65.3%) patients used ICS in the year prior to the PCR test. Overall, 996 (9.42%) patients were found to be positive for SARS-CoV-2. With regard to the first study objective, no significant association was found between ICS use and SARS-CoV-2 infection; compared to nonusers, the adjusted odds ratios were 1.06 (95% CI 0.91–1.23) for recent ICS users and 0.93 (95% CI

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The use of ICS is safe and people living with #asthma should continue to take their prescribed medication as usual during the #COVID19 pandemic https://bit.ly/3rOYIL2

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TABLE 1 Multivariable odds ratios for the association between inhaled corticosteroid (ICS) use and SARS-CoV-2 infection, and multivariable hazard ratios (HRs) for the association between ICS use and moderate–severe COVID-19 and the composite of moderate–severe COVID-19 and all-cause mortality, among asthmatic patients

Variables	Association of ICS use with SARS-CoV-2 infection OR (95% CI), p-value	Association of ICS use with COVID-19 severity and mortality	
		Moderate–severe COVID-19 HR (95% CI), p-value	Composite of moderate–severe COVID-19 and all-cause mortality HR (95% CI), p-value
Age	1.00 (0.99–1.00), 0.799	1.03 (1.02–1.05), <0.001	1.04 (1.02–1.05), <0.001
Female sex	0.92 (0.80–1.06), 0.270	0.64 (0.41–1.00), 0.050	0.67 (0.44–1.04), 0.073
Arab ethnicity[#]	2.44 (2.09–2.86), <0.001	2.00 (1.28–3.14), 0.003	1.85 (1.20–2.86), 0.006
Diabetes	1.18 (0.97–1.44), 0.093	0.80 (0.49–1.29), 0.352	0.79 (0.50–1.26), 0.320
Hypertension	0.99 (0.82–1.21), 0.940	2.02 (1.17–3.51), 0.012	2.05 (1.21–3.50), 0.008
Obesity	1.21 (1.04–1.40), 0.013	1.75 (1.10–2.78), 0.019	1.68 (1.08–2.61), 0.021
Ischaemic heart disease	0.99 (0.77–1.27), 0.928	0.92 (0.53–1.58), 0.758	0.99 (0.59–1.66), 0.981
Hospitalisation in the prior year	0.86 (0.73–1.02), 0.79	1.86 (0.88–3.92), 0.104	1.80 (0.89–3.64), 0.102
Recent systemic corticosteroid use[¶]	0.89 (0.72–1.10), 0.279	1.54 (0.93–2.52), 0.090	1.41 (0.86–2.30), 0.172
ICS use in the prior year			
None	Ref.	Ref.	Ref.
Recent[¶]	1.06 (0.91–1.23), 0.483	0.98 (0.60–1.58), 0.927	0.90 (0.57–1.41), 0.64
Former[+]	0.93 (0.77–1.13), 0.467	0.86 (0.46–1.62), 0.648	0.80 (0.44–1.45), 0.457

Multivariable models were adjusted for age, sex, ethnicity, diabetes, hypertension, ischaemic heart disease, obesity, hospitalisation in the prior year and systemic corticosteroid use. [#]: compared to Jewish ethnicity; [¶]: ⩽90 days; [+]: 90–365 days.

0.77–1.13) for former ICS users (table 1). With regard to the second study objective, ICS use was not associated with increased risk of moderate–severe COVID-19; compared to nonusers the adjusted hazard ratios were 0.98 (95% CI 0.60–1.58) for recent ICS users and 0.86 (95% CI 0.46–1.62) for former ICS users (table 1). The results were similar for the composite of moderate–severe COVID-19 and 90-day all-cause mortality (table 1).

Recent studies suggest that ICS suppress SARS-CoV-2 replication and reduce the expression in bronchial epithelial cells of angiotensin-converting enzyme 2 receptor, which mediates SARS-CoV-2 cell entry [5–8]. Further, the available data from most of the epidemiological studies generally suggest that ICS are not an independent risk factor for increased SARS-CoV-2 infectivity or COVID-19 severity, advising that ICS treatment in patients with asthma is safe and should be continued during the COVID-19 pandemic [9–13]. However, other studies reported some conflicting results, such the study by Schultze *et al.* [14] that by using the OpenSAFELY platform, reported an increased risk of death from COVID-19 among people with asthma on high-dose ICS. Although various sensitivity analyses indicated that this increased mortality risk could be explained by unmeasured confounders, including disease severity and risk factors for severe COVID-19, the question whether regular ICS therapy for asthma is safe in the current SARS-CoV-2 pandemic is still not completely answered. The results of our study suggest that, in asthmatic patients, recent and former use of ICS are not associated with increased risk of SARS-CoV-2 infection nor with increased risk of COVID- 19 severity or mortality.

The limitations of the study include lack of data about asthma severity, and limitations related to the observational and retrospective nature of the study.

In summary, our study adds to the strength of the current evidence and the current recommendation that the use of ICS is safe, and asthmatic patients should continue to take their prescribed asthma medication as usual, including ICS alone or in combination with a long-acting β_2-agonist, during the COVID-19 pandemic.

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