Early View

Research letter

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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 which 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 increase the risk of SARS CoV-2 infection and affect COVID-19 severity and mortality.

In the current study, we examined two objectives; i) the association between ICS use and SARS-CoV-2 infection in asthmatic patients, using a test negative case-control study approach, and ii) 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 computerized database of CHS to retrospectively identify all ≥ 18 -year-old with an asthma diagnosis (ICD-9, 493.xx) who have seen at least twice by a Pulmonologist in the recent 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 WHO definitions (4).

ICS use was determined using the CHS pharmacy records using the Anatomical Therapeutic Chemical (ATC) classification codes. Based on the timing of ICS prescriptions filled in the previous year patients were classified into three categories; none vs. recent (≤ 90 days) vs 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, ischemic heart disease, obesity, hospitalization in the prior year, and systemic corticosteroids (SCS) 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 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 no users the adjusted ORs were 1.06 (95% CI, 0.91-1.23) for recent ICS users and 0.93 (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 no users the adjusted HRs were 0.98 (0.60-1.58) for recent ICS users and 0.86 (0.46-1.62) for former ICS users (Table 1). The results were similar for the composite of moderate-severe COVID-19 and 90 days all-cause mortality (Table 1).

Recent studies suggest that ICS suppress SARS-CoV-2 replication and reduced angiotensin converting enzyme 2 (ACE2) receptor, which mediate SARS-CoV-2 cell entry, expression in bronchial epithelial cells (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 confounder 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 long acting beta₂ agonist, during the COVID-19 pandemic.

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Table 1: Multivariable* ORs for the association between inhaled corticosteroids use (ICS) and SARS-CoV-2 infection, and multivariable* 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 asthmatics

Variables	Association of ICS use with SARS-CoV-2 infection <i>OR (95% CI), p value</i>	Association of ICS use with COVID-19 severity and mortality	
		moderate-severe COVID-19 <i>HR (95% CI), p value</i>	Composite of moderate-severe COVID-19 and all-cause mortality <i>HR (95% CI), p value</i>
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
Arabs (compared to Jews)	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
Ischemic 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
Hospitalization 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 corticosteroids use (in the prior 3 months)	0.89 (0.72-1.10), 0.279	1.54 (0.93-2.52), 0.090	1.41 (0.86-2.30), 0.172
Inhaled corticosteroids use in the prior year			
None	Reference	Reference	Reference
Recent (prior 3 months)	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 (3-12 months)	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, ischemic heart disease, obesity, hospitalization in the prior year, and systemic corticosteroids (SCS) use