COVID-19, Asthma, and Inhaled Corticosteroids (ICS): Another Beneficial Effect of ICS?

Tania Maes, PhD[1], Ken Bracke, PhD[1] and Guy G. Brusselle, PhD, MD[1,2]

Institutional Affiliations

[1]Department of Respiratory Medicine, Ghent University Hospital, Gent, Belgium

[2]Departments of Epidemiology and Respiratory Medicine, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands

Corresponding author:

Guy G Brusselle, Ph.D., MD

Department of Respiratory Medicine, Ghent University Hospital

Corneel Heymanslaan 10, B-9000 Gent, BELGIUM

Guy.brusselle@ugent.be

Phone 0032 9 332 2672

Authors Contributions:

TM and GB have jointly written the editorial; KB coordinates the human lung tissue bank at Ghent University Hospital and has performed the ACE2 gene expression analysis; all authors have given final approval for the manuscript to be submitted.

Funding: The Department of Respiratory Medicine (Ghent University) is funded by a concerted research action of Ghent University (BOF-/GOA-01G00819) and the Fund for Scientific Research in Flanders (Projects G053516N, G052518N and G041819N, EOS project G0G2318N).

Key words: asthma, COVID-19, SARS-COV-2, inhaled corticosteroids

Word count: 1057

AJRCCM Articles in Press. Published May 21, 2020 as 10.1164/rccm.202005-1651ED

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a real pandemic. After a median incubation period of 5 days the disease occurs in different stages, inducing upper and lower airway responses in mild disease (80 to 90% of patients) and progressing to bilateral pneumonia in severe disease (10 to 20%) [1-3]. A subgroup of patients with severe COVID-19 develops Acute Respiratory Distress Syndrome (ARDS), requiring mechanical ventilation on intensive care. COVID-19 patients with pre-existing comorbid conditions such as chronic respiratory diseases have worse disease outcomes, including a higher incidence of the need for hospitalization, ICU admission and mortality [3,4]. However, it remains to be further investigated how pre-existing chronic inflammatory airway diseases, such as asthma and COPD, and their treatment might modify the risk for SARS-CoV-2 infection and development of COVID-19. Approximately 300 million individuals worldwide have asthma [5]. Considering that a significant proportion of asthmatics is confronted with COVID-19, it is crucial to understand which asthma patients are particularly at risk and how inhaled corticosteroids (ICS) - the cornerstone of asthma treatment - may influence morbidity and mortality associated with COVID-19. Long-term treatment with systemic corticosteroids (e.g. in transplant patients) is immunosuppressive, increasing the risk and severity of viral infections. Due to the potential risk for worse disease outcomes, the World Health Organization (WHO) does not recommend systemic corticosteroid treatment in COVID-19 [6], unless if indicated for other reasons such as acute asthma or COPD exacerbations requiring a short course of oral corticosteroids. These recommendations have caused doubt and uncertainty among asthma patients and physicians on whether ICS therapy should be maintained during this pandemic. However, withdrawal of ICS treatment puts asthma patients at risk of severe exacerbations. A recent meta-analysis on COVID-19 outcomes in patients with chronic respiratory diseases using ICS concluded that there is currently insufficient evidence to abandon the well-established ICS-treatment in asthma [7]. There is thus an urgent need to elucidate demographic and clinical characteristics which determine disease outcomes of COVID-19 in asthma, to investigate the impact of ICS and to unravel the underlying pathogenic mechanisms.

AJRCCM Articles in Press. Published May 21, 2020 as 10.1164/rccm.202005-1651ED

The elegant study by M. Peters, J. Fahy and the Severe Asthma Research Program-3 (SARP-3) investigators, here, provides important insights in the complex interplay between asthma, ICS, SARS-CoV-2 infection and COVID-19 [8]. The authors hypothesized that differences in the expression of angiotensin converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) may modulate the individual susceptibility to and clinical course of SARS-CoV-2 infection, and thus identify asthma subgroups at risk for COVID-19 morbidity. Whereas the spike protein of SARS-CoV-2 binds to ACE2 as receptor during viral attachment to host cells, viral entry is also facilitated by priming of the spike protein by the membrane-bound protease TMPRSS2 [9]. By investigating induced sputum samples from 330 participants of the SARP-3 program, a large and well characterized cohort of asthma subjects (60% severe asthma), and 79 healthy controls, Peters *et al.* made three major discoveries. First, they found that there were no significant differences in gene expression of ACE2 in sputum between asthma and healthy subjects, suggesting that asthma subjects might not be at increased risk of COVID-19. This contrasts with the increased expression of intercellular adhesion molecule 1 (ICAM-1) in sputum of asthmatics. ICAM-1 is the receptor for rhinovirus, which causes only limited upper airway symptoms in healthy individuals, but can elicit protracted lower airway symptoms and severe exacerbations in asthmatics. Second, they discovered that male gender, African American ethnicity and a history of diabetes mellitus are associated with an elevated ACE2 and TSMPRSS2 mRNA expression in induced sputum. Since people with diabetes have worse outcomes in severe COVID-19 [2,3,10], these findings suggest that increased expression of SARS-CoV-2 associated genes may facilitate viral infection and underscore that asthmatics with one or more of these characteristics should be monitored for worse outcomes of COVID-19.

Thirdly and most importantly, they demonstrate that - in contrast to systemic corticosteroids - the use of ICS in asthma subjects was dose-dependently associated with reduced ACE2 and TMPRSS2 mRNA expression. If these intriguing findings are confirmed at the protein level, they may have important clinical implications. ACE2 expression has been predominantly reported in epithelial cells [11-13], which are a minor fraction within induced sputum which mainly samples inflammatory cells in

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the lower airways. How expression of SARS-CoV-2 associated genes is modulated in specific airway inflammatory cells in asthma and whether this affects viral entry and infectivity requires further investigation. Moreover, it is important to evaluate the expression of ACE2 also in lung tissue since this is the predominant place of injury in severe COVID-19. In our lung tissue bank at Ghent University Hospital, we studied ACE2 gene expression in lung resection specimens of Caucasian subjects with and without obstructive airway disease (OAD), encompassing asthma and/or COPD, and investigated whether ACE2 gene expression was associated with ICS use (Fig 1). Whereas ACE2 mRNA expression in lung tissue was significantly increased in (current or former) smokers with COPD, it was not altered in subjects with asthma or Asthma COPD Overlap (ACO) as compared with controls without OAD (Fig1A). However, pulmonary gene expression of ACE2 did not differ in ICS-treated and non-ICS-treated OAD subjects (Fig1B). These results need to be replicated in larger prospective studies and in other (non-Caucasian) ethnicities. The divergent effects of ICS use on ACE2 expression between both studies might be due to differences in respiratory compartment (induced sputum *versus* lung tissue) or patient population (non-smoking asthmatics *versus* smokers with COPD).

In conclusion, the crucial findings from Peters *et al.* support the recommendation that in patients with asthma using ICS, this treatment should be continued since ICS are the cornerstone of asthma management, reducing exacerbations and asthma mortality, and are associated with decreased expression of ACE2, the receptor of SARS-CoV-2, in induced sputum. To what extent up- or down-regulation of ACE2 expression in sputum, airways or lungs has clinical consequences on infectivity or outcomes of Covid19 needs to be elucidated. In subjects without asthma (or exacerbation-prone COPD), ICS should not be started since ICS use does not seem to influence ACE2 expression in lung tissue. However, we eagerly await the results of randomised controlled trials assessing the efficacy and safety of ICS in treating COVID-19 in patients with and without chronic airway diseases (see https://clinicaltrials.gov).

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Acknowledgements

The authors acknowledge S. Wijnant, M. Jacobs and H. Van Eeckhoutte and the technical staff of the Department of Respiratory Medicine for their efforts in collecting the data that are presented in this manuscript.

Conflict of interest

The authors declare no conflicts of interest related to this editorial.

G. Brusselle has received speaker's fees and participated in advisory boards of AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Sanofi and Teva. T. Maes has participated in an advisory board from GlaxoSmithKline and is shareholder of Oryzon Genomic and Mendelion Lifesciences SL. K. Bracke has participated in an advisory board from GlaxoSmithKline.

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Figure Legend

Figure 1. ACE2 mRNA expression in human lung tissue and effect of inhaled corticosteroids (ICS). **A)** ACE2 gene expression in lung tissue from controls (n: 61), asthma/ACO (n: 7) and COPD (GOLD stage II) (n: 38). **B)** ACE2 gene expression in controls (no OAD, no ICS use, n: 56), in subjects with OAD not using ICS (n: 23) and in subjects with OAD using ICS (n: 25). ACE2: Angiotensin-converting Enzyme-2; ACO: Asthma COPD Overlap; OAD: Obstructive Airway Diseases (asthma, ACO or COPD).

Lung resection samples were obtained with approval from the ethical committee of Ghent University hospital (2016/0132); all participants provided written informed consent. Processing for RNA and quantitative reverse transcription-polymerase chain reaction (RT-PCR) analysis was performed as described previously[14-15]. ACE2 mRNA expression was normalized to the expression of three reference genes.

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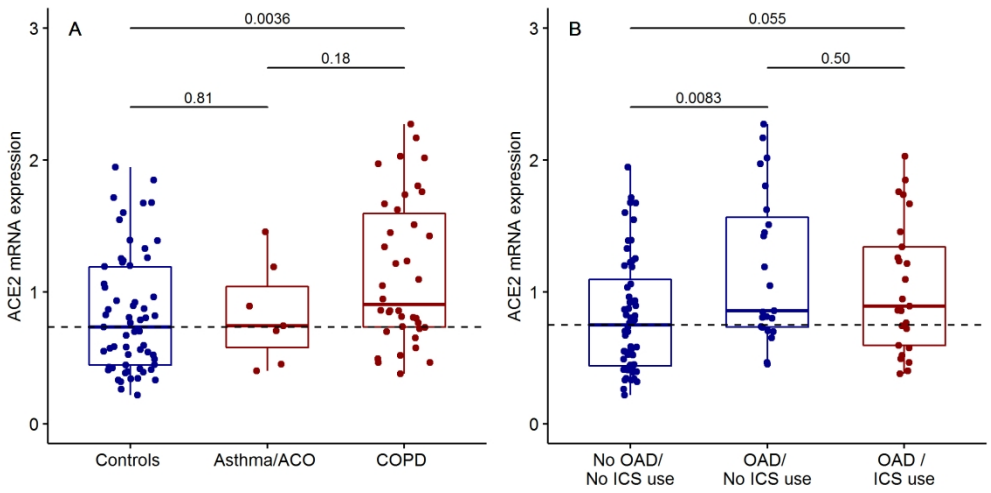

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