Use of inhaled corticosteroids in asthma and coronavirus disease 2019

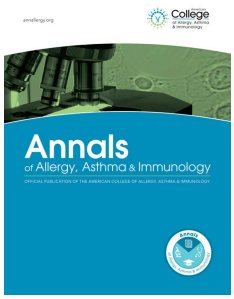
Lipworth, Brian; Chan, Rory; Kuo, Chris

Published in:
Annals of Allergy, Asthma and Immunology

DOI:
10.1016/j.anai.2020.06.026

Publication date:
2020

Journal Pre-proof



Use of inhaled corticosteroids in asthma and COVID-19 : Keep calm and carry on

Dr Brian Lipworth, MD, Dr Rory Chan, MBCHB, Dr Chris RuiWen Kuo, MBChB

PII: S1081-1206(20)30433-6

DOI: https://doi.org/10.1016/j.anai.2020.06.026

Reference: ANAI 3295

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 18 May 2020

Revised Date: 9 June 2020

Accepted Date: 15 June 2020

Please cite this article as: Lipworth B, Chan R, RuiWen Kuo C, Use of inhaled corticosteroids in asthma and COVID-19 : Keep calm and carry on, *Annals of Allergy, Asthma and Immunology* (2020), doi: https://doi.org/10.1016/j.anai.2020.06.026.

Use of inhaled corticosteroids in asthma and COVID-19 : Keep calm and carry on

Dr Brian Lipworth MD
Dr Rory Chan MBCHB
Dr Chris RuiWen Kuo MBChB

Scottish Centre for Respiratory Research
Ninewells Hospital and Medical School
University of Dundee ,DD1 9SY
Scotland ,UK

b.j.lipworth@dundee.ac.uk

Contributors statement:

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to permit this article (if accepted) to be published in Annals Allergy Asthma and Immunology .

BJL had the idea and is responsible for the overall content as guarantor. BJL, RC, and CRK all performed the literature search and contributed to the writing of the article. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

There was no funding involved in preparing this article

Conflicts of interest:
Dr. BJ Lipworth reports grants and personal fees from Sanofi, grants and personal fees from AstraZeneca, grants and personal fees from Teva, personal fees from Cipla, personal fees from Glenmark, personal fees from Lupin, personal fees from Vectura , personal fees from Dr Reddys , personal fees from Novartis, grants, personal fees and other from Chiesi ,relevant to the submitted work ,personal fees from Circassia ,personal fees from Thorasys outside of the submitted work and Son of BJL is employee of AstraZeneca.
Dr. Chan has no relevant conflicts of interest.
Dr. Kuo reports personal fees from AstraZeneca and Chiesi relevant to the submitted work ,and from Circassia outside of the submitted work

Word Count 806

Inhaled corticosteroids (ICS) are used as anti-inflammatory controller therapy given either alone or combination with long acting bronchodilators for persistent asthma . The present COVID-19 pandemic has inevitably focussed attention as to whether ICS might predispose to SARS-CoV-2 infection , especially in older ,male, obese, smokers with comorbidities including chronic lung disease who are prone to more severe COVID-19 infection and worse outcomes. In the later stage of COVID-19 infection there is an acute inflammatory cytokine cascade including interleukin 1-beta (IL1-β) , interleukin-6 (IL6) and tumour necrosis factor alpha (TNF-α). This in turn results in a hyper-inflammatory and coagulopathy state with acute respiratory distress syndrome and an attendant high morality rate. A United Kingdom database of 17 million adult patients reported the .presence of asthma without recent oral corticosteroid use was associated with a 10% increased risk of hospital death with COVID-19 , which doubled to 20% in those with recent oral corticosteroid (OCS) use. The present evidence does not support the use of systemic corticosteroids for treating COVID-19. .Although ICS exhibit dose related systemic absorption from the lung the degree of attendant systemic glucocorticoid activity in asthma is relatively low compared to OCS. Whether or not ICS might confer a different risk-benefit profile in COVID-19 is presently unknown . Here we discuss the pros and cons of using ICS in relation to COVID-19 (Figure) .

Concerns around the use of ICS in asthma in COVID-19 arise from the potential immunosuppressive effects in the lungs especially in the presence of impaired host defence. The premise here is that corticosteroids may promote viral replication, delayed viral clearance and also predispose to secondary bacterial infection. In support of this a Canadian cohort study of asthma patients demonstrated that current exposure to ICS was accompanied by a 45% relative increase in bacterial pneumonia

risk . In contrast a study in H1N1 influenza A infection among 1520 UK hospitalized patients found those with asthma were 49% less likely to require intensive care support or to die than those without asthma , which was attributed to ICS use.

This in turn suggests the possibility of a class effect of ICS by protecting against viral insults in asthma patients, which might be due to downstream cytokine suppression . In favour of this hypothesis in vitro suppressive effects were seen with budesonide on replication of coronavirus HCoV-229E (the common cold) and on production of cytokines including IL6 ,IL8 and interferon-β ,using primary cultures of human nasal and tracheal epithelial cells ,while another in vitro study showed systemic suppression of IL6 by budesonide[1, 2]. This could be particularly relevant as raised levels of IL6 are strongly related to worse outcomes in patients with severe COVID-19 pneumonia with evidence of hyper-inflammation. In addition it has been shown that in sputum cells from 330 asthma patients the use of ICS was associated with reduced gene expression of angiotensin converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) , both of which are pivotal membrane bound receptors involved in host cell entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. Moreover in patients with type 2 asthma exposure to exogenous interleukin-13 in ex vivo primary airway epithelial cells decreases ACE2 and increases TMPRSS2 expression [4]. Whether altered cell receptor expression might translate into reduced viral load with ICS therapy is unknown .

There are also preliminary data to perhaps suggest a more specific salutary effect of ICS with COVID-19 . In vitro experiments have shown that ICS may not all be same in that low concentrations of ciclesonide and mometasone but not fluticasone ,budesonide or beclomethasone appear to suppress replication of SARS-CoV-2 , to the same degree as lopinavir .[5] The inhibitory action of ciclesonide on replication of

SARS-CoV-2 was mediated via non-structural protein 15 (NSP15) . There have been case reports of COVID-19 pneumonia successfully treated with inhaled ciclesonide but no data yet from ongoing randomised controlled trials (NCT04416399, NCT04381364, NCT04377711). In respect of COVID pneumonia inhaled ciclesonide achieves high alveolar deposition and prolonged lung retention due to formation of intracellular fatty acid conjugates, in addition to producing minimal systemic adverse effects at higher doses .

As an initial step health informatics studies may help to elucidate if ICS might alleviate or worsen COVID-19 outcomes in asthma patients, in particular looking at dose response effects . Randomized controlled trials may also be warranted in patients who do not have asthma perhaps to see if secondary prevention with ICS including ciclesonide or mometasone can prevent progression of early COVID infection in susceptible older patients with comorbidities . Meanwhile for patients with asthma the current guidance is to continue taking their ICS containing controller therapy because ultimately this may also confer optimal protection against viral infections including SARS-CoV-2 and also prevent eosinophilic related exacerbations .

Figure Legend

Depicts putative positive and negative effects of inhaled corticosteroids in COVID-19 infection on (a) viral replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) including specific effects of mometasone furoate and ciclesonide on non structural protein 15 (NSP15), (b) reduced expression of angiotensin converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) , (c) suppression of pro-inflammatory cytokines including interleukin-6 (IL6) , (d) promotion of

75 secondary bacterial infection , (e) effects on neutrophils and eosinophils , (f)

76 suppression of adrenal secretion of cortisol and aldosterone

References

1. Yamaya M, Nishimura H, Deng X, et al. Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus HCoV-229E replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells. *Respir Investig.* 2020;58:155-168.

2. Suda K, Tsuruta M, Eom J, et al. Acute lung injury induces cardiovascular dysfunction: effects of IL-6 and budesonide/formoterol. *American journal of respiratory cell and molecular biology.* 2011;45:510-516.

3. Peters MC, Sajuthi S, Deford P, et al. COVID-19 Related Genes in Sputum Cells in Asthma: Relationship to Demographic Features and Corticosteroids. *Am J Respir Crit Care Med.* 2020.

4. Kimura H, Francisco D, Conway M, et al. Type 2 Inflammation Modulates ACE2 and TMPRSS2 in Airway Epithelial Cells. *Journal of Allergy and Clinical Immunology.*

5. Matsuyama S KM, Nao N, Shirato K, Ujike M, Kamitani W, et al. The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15. *bioRxiv.* 2020:2020.03.11.987016.

-