Official Journal of the Asian Pacific Society of Respirology
Respirology 25th
APSR

COMMENTARY

Attenuating COVID-19 infection and inflammation: Lessons from asthma

Key words: asthma, corticosteroids, COVID-19, exacerbations.

In the turmoil surrounding the current global pandemic, it is often forgotten that coronavirus disease 2019 (COVID-19) is a common cold virus, albeit with a crown. Infection by COVID-19 has several unique features, but two key aspects dominate the disease. First, as a common cold virus, it has the classic ability of this virus group to spread very readily person-to-person despite virtually any intervention aimed at eradicating transmission. Second, initial upper airway involvement progresses in susceptible persons to lung infection with uncontrolled virus loads leading to mounting inflammation resulting in respiratory impairment and failure.[1,2] What is not readily appreciated is that asthma exacerbations occur in an almost identical setting: a common cold virus infection in susceptible persons is followed by increased virus loads, lung infection and inflammation with subsequent respiratory compromise. Given these similarities, are there valuable lessons applicable to COVID-19 to be learned from a long history of effective treatment for virus-induced asthma exacerbations?

More than 200 different viruses can cause a common cold but rhinoviruses, coronaviruses, respiratory syncytial and parainfluenza viruses are implicated in the majority of colds. Until recently, their importance as infectious agents was underestimated despite landmark studies in the early 1990s demonstrating that asthma exacerbations are predominantly triggered by common colds.[3] Studies in individuals with asthma demonstrated that spread to the lung was followed by inflammation, airway obstruction, heightened responsiveness and respiratory compromise.[4] However, at an early stage, it was clear that preventing infection was challenging and specific treatments for common cold viruses have remained elusive. Other strategies had to be devised in order to counter acute detrimental effects of these viruses on the lung.

Asthma exacerbations can lead to death, often in young persons, and anti-inflammatory treatment with oral or parenteral corticosteroids (CS) effectively mitigate exacerbations.[5] Blunting the detrimental inflammatory impacts of virus infection made it possible to reduce mortality and consequently CS have remained in widespread use to treat virus-associated asthma exacerbations. A key message has been that controlling inflammation was sufficient to restore reasonable lung function whilst host immune responses ultimately eliminated the virus.

Understandably, much scientific endeavour and the public imagination have been fixated on the goal of rapid COVID-19 vaccine development. However, this is challenging and success is not guaranteed (although potent induction of neutralizing antibody responses in early reports is an encouraging sign). Attempts to find effective vaccines fail. For example, despite spirited efforts, no vaccine has proven effective to date to prevent human immunodeficiency virus (HIV) infection.[6] Given the considerable obstacles facing vaccine developers, strategies aimed at blunting COVID-19-associated inflammation should also be deliberately pursued.

Are there established as well as novel anti-inflammatory compounds that can be used in COVID-19 infection? Currently, only systematic CS are recommended to treat patients who are severely ill with COVID-19 infection as they have been clearly shown to reduce mortality in those needing respiratory support and to reduce the need for mechanical ventilation.[7] Other compounds considered for repurposing include chloroquine/hydroxychloroquine, Janus kinase (JNK) inhibitors (baricitinib and tofacitinib), interleukin (IL)-6 inhibitors (tocilizumab and sarilumab), IL-1 inhibitors (anakinra and canakinumab) and colchicine.[8,9] Many of these compounds are being evaluated in rigorous randomized controlled trials (RCT).[10] Hydroxychloroquine has been shown to be ineffective when given late in severe disease in hospitalized patients, likely because any antiviral/anti-inflammatory effects are outweighed by adverse events in these very ill people.[11] Tocilizumab, in particular, has shown early promise as a way of reducing IL-6-mediated hyperinflammation, albeit in small studies.[12] Other compounds merit investigation including pirfenidone[13] and colchicine,[14] both agents with broad-ranging anti-inflammatory activities comparable to CS. Pirfenidone has also been formulated for inhalation,[15] potentially limiting adverse effects. Baricitinib has substantial potential efficacy as it can reduce both inflammation (JNK inhibition) and virus infection (inhibits clathrin-mediated endocytosis).[16] The need to expand pioneering research into other potentially promising compounds is urgent.

A second key message that emerges from studying asthma is the importance of deficient antiviral immunity[17] in driving inflammation and adverse clinical outcomes. Exactly the same is almost certain to be true of COVID-19. We have recently reported that adverse outcomes in males with COVID-19 are likely to be related in large part to deficient innate antiviral immune responses.[18] Interferon (IFN)-β has been shown to prevent adverse outcomes and enhance recovery when given early in COVID-19, and to reduce mortality when given later in severe COVID-19.[19,20] We have known for 10 years that azithromycin doubles IFN production by

doi: 10.1111/resp.13961

virus-infected bronchial epithelial cells,[21] and it has been shown both to prevent[22] and to treat[23] virus-induced wheezing episodes in asthma. Results of current RCT of azithromycin (to boost antiviral immunity), given early in COVID-19 when this approach is likely to have maximal benefit and thus reduce severe outcomes, are eagerly awaited.

In summary, highly successful treatments of virus-associated inflammation during asthma exacerbations are those that mitigate effects of high virus loads driving lung inflammation. For COVID-19 infection, the parallels are obvious. In the context of the current pandemic, it highlights the urgent need to research and validate both existing and novel antiviral and anti-inflammatory compounds.

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Disclosure statement: P.G.B. is employed by Monash Health, and affiliated with Monash University and Hudson Institute of Medical Research, Melbourne, Australia. The views expressed are those of the author only. S.L.J. is a National Institute of Health Research (NIHR) Emeritus Senior Investigator and is funded in part by European Research Council Advanced Grant 788575, the Asthma UK Clinical Chair (grant CH11SJ) and by the NIHR Imperial Biomedical Research Centre (BRC). The views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care.

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