Asthma and COVID-19: is asthma a risk factor for severe outcomes?

Sebastian L. Johnston MBBS PhD

National Heart and Lung Institute, Imperial College London, United Kingdom

Corresponding author:

Sebastian L Johnston

Professor of Respiratory Medicine & Allergy

National Heart and Lung Institute

Imperial College London

Norfolk Place

London W2 1PG

United Kingdom

Tel: +44 20 7594 3764

e-mail: s.johnston@imperial.ac.uk

Funding SLJ is a National Institute of Health Research (NIHR) Emeritus Senior Investigator and is funded in part by European Research Council Advanced Grant 788575. This research was supported by the NIHR Imperial Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Word count 1261 words.

Key words: COVID-19, asthma

When I first read the manuscript that accompanies this editorial, upon its online publication on February 19th 2020(1), COVID-19 had already killed 2118 people in China, but only one person in Europe – an 80-year-old tourist from China, who died in France on the 15th February. I read the manuscript with grim fascination, as it was clear that SARS-CoV-2 had spread very rapidly in China which already had 74,576 cases and in South Korea which already had 58 cases, and that it was then invading Europe also, as France already had 12 cases, Germany 16, the UK 9, Italy 3, Spain 2 and other countries too. It was already clear that unless we did something as drastic as the Chinese were doing to limit spread of SARS-CoV-2, we would be subject to a catastrophe as terrible as the one Wuhan was then experiencing. I did not then think that by the time of writing (4th April, only 6 weeks later) COVID-19 mortality in four major European countries would already have exceeded that in China(2). Such shocking statistics bring into sharp focus the need to identify risk factors for severe outcomes with COVID-19, and if possible, to favourably modify any risk factors that are amenable to modification.

We have known for 18 years that people with asthma are at risk of more severe outcomes with common cold virus infections than are people without asthma(3), and we also know that if asthma is not well controlled, virus-induced exacerbation severity is dramatically worsened in relation to the degree of lack of control(4). We also know that many people with asthma have deficient and delayed innate anti-viral immune responses, with deficiency and delay in lung cell interferon (IFN)-α(5), IFN-β(6) and IFN-λ(7) responses reported in many studies, and deficiency of the latter IFN clearly related to increased asthma exacerbation severity(7). Based on this evidence it would seem inevitable that asthma should be identified as a risk factor for severe outcomes in COVID-19.

The manuscript by Zhang et al reports clinical characteristics of 140 cases of community acquired COVID-19 in Wuhan, China, with 82 cases classified as non-severe, and 58 as severe. Surprisingly, no self-reported allergic disease including asthma, allergic rhinitis, food allergy, atopic dermatitis and other type 2 allergic disease was documented among the 140 cases. A similar report comparing PCR-positive and PCR-negative cases reported only a single case of asthma among 290 laboratory confirmed hospitalised COVID-19 cases(8). Asthma has not yet been identified as a risk factor for

severe outcomes in COVID-19 in any of the larger case series reported to date either(9). This is a surprise, but chronic respiratory disease had the third highest case fatality ratio, after cardiovascular disease and diabetes, in the largest case series (44,672 confirmed COVID-19 cases) reported to date(10). It is probable that cases of asthma were among those 511 chronic respiratory disease cases, but this information was not provided. I believe that as more case series with larger numbers of people with asthma included are reported, that asthma (particularly asthma in older people, as age has already been identified as the most important risk factor) will likely emerge as a significant risk factor for severity in COVID-19.

If that is the case, what can we do about mitigating this risk? Of course, even more than in "normal" times patients with asthma should refrain from smoking, as smoking has been clearly associated with worse outcomes in COVID-19(11). Since poor asthma control is a risk factor for greater virus-induced exacerbation severity(4), maintaining optimal asthma control will inevitably reduce risk of severe outcomes in COVID-19. Since all methods of optimising asthma control, whether they be inhaled steroids, combination inhaled steroid plus long acting bronchodilator therapies, or monoclonal antibody therapies, have been shown to substantially reduce exacerbation risk (the great majority of which are virus-induced), all standard asthma therapies should continue to be used to optimise asthma control, with certainty that this will reduce risk of adverse outcomes with COVID-19. Specific concerns have been raised in relation to steroid therapy and possible risk of adverse outcomes in COVID-19(12), however, since allergic airway inflammation in the lung, as occurs in asthma, will suppress anti-viral immunity in the lung(13), suppressing allergic airway inflammation with a topical steroid will restore antiviral immunity, so inhaled steroid treatment should be initiated/continued/increased as clinically indicated. These recommendations are supported by a recently published statement from the EAACI Section on Pediatrics(14) which concludes that "optimal disease control of allergic, asthmatic and immunodeficient children should be sought according to usual treatment guidelines".

One further specific method of modifying risk of severe outcomes with COVID-19 for people with asthma deserves special focus. Azithromycin 500mg three times per week has been shown to reduce asthma exacerbation frequency by ~40% and to improve quality of life in people with asthma that was

not adequately controlled on standard inhaler therapy(15). The mechanisms of action of azithromycin in this study were not elucidated, but since we know that the great majority of asthma exacerbations are virus-induced, it seems likely that effects on antiviral immunity may have been involved.

We previously reported that azithromycin (but not erythromycin or telithromycin) substantially augments IFN-β and IFN-λ production from rhinovirus-infected human bronchial epithelial cells *in vitro*(16). IFN-β and IFN-λ-induction by azithromycin in virus-infected bronchial epithelial cells *in vitro* was subsequently confirmed in a separate study, which also confirmed this property was variable among the 225 novel macrolides studied (potent in some, absent in others). One related macrolide induced IFNs ~5-fold, and was shown to significantly (*P*=0.023) suppress virus replication in bronchial epithelial cells from people with asthma(17).

Anti-viral IFN production by virus-infected respiratory cells will be critical to host defense mediated by innate anti-viral immunity against SARS-CoV-2, a virus that we have no acquired immune response to. Thus, treating/preventing COVID-19 severity with azithromycin in people with asthma in order to substantially boost IFN production by respiratory cells when infected with SARS-CoV-2, is clearly likely to be highly effective at reducing risk of severe outcomes. This conclusion is strongly supported by high quality clinical trial evidence that azithromycin prevents asthma exacerbations (which are mostly virus-induced)(15) and is effective in prevention of severe lower respiratory tract illnesses (respiratory viral infections) in preschool children(18).

This conclusion is also supported by a study in COVID-19 patients without asthma (at least asthma was not mentioned in the entire manuscript), which found substantially greater benefit in SARS-CoV-2 virus load clearance in 6 patients treated with both azithromycin and hydroxychloroquine, compared to those treated with hydroxychloroquine alone (though the authors' rationale for giving azithromycin was "to prevent bacterial super-infection", not because of its virus-specific IFN-inducing properties, which they did not mention)(19).

I would not normally make treatment recommendations in the absence of controlled clinical trials. However, these are not normal times. My recommendations to people with asthma and those treating them are most importantly to optimize asthma control with standard therapies, but if asthma control is not optimal despite appropriate use of standard therapies, to have a low threshold for starting azithromycin prophylaxis (because of its innate antiviral (IFN-boosting) property, at this time of enormous threat from COVID-19.

We do not have the time to wait for controlled clinical trials. There are 10 trials registered on clinicaltrials.gov that plan to investigate azithromycin in COVID-19 (none related to asthma). Nine had not started recruitment at the time of writing. The only one that had started recruitment is studying azithromycin in hospitalized people requiring escalation to critical care. I do not wish that to happen to people with asthma when prevention or early treatment is likely to be efficacious.

Conflict of interest statement:

Dr. Johnston reports personal fees from Virtus Respiratory Research, personal fees from Myelo TherapeuticsÐmbH, personal fees from Concert Pharmaceuticals, personal fees from Bayer, personal fees from Synairgen, personal fees from Novartis, personal fees from Boehringer Ingelheim, personal fees from Chiesi, personal fees from Gerson Lehrman Group, personal fees from resTORbio, personal fees from Bioforce, personal fees from Materia Medical Holdings, personal fees from PrepBio Pharma, personal fees from Pulmotect, personal fees from Virion Health, personal fees from Lallemand Pharma, personal fees from AstraZeneca, outside the submitted work; In addition, Dr. Johnston has a patent Wark PA, Johnston SL,Ðolgate ST, Davies DE.Únti-virus therapy forÐespiratory diseases.ÐK patent applicationÐo. GB 0405634.7, 12Ðarch 2004. with royalties paid, a patent Wark PA, Johnston SL,Ðolgate ST, Davies DE.Ðnterferon-Beta forÚnti-Virus Therapy forÐespiratory Diseases.Ðnternational PatentÚpplication No. PCT/ÐB05/50031, 12 MarchÒ004. with royalties paid, and a patent Davies DE, Wark PA,Ðolgate ST, JohnstonÐL. Interferon LambdaÐherapy for theÐreatment ofÐespiratory disease. UKÐatent application No.Ö779645.9, grantedÑ5th August 2012. licensed.

References

1. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020.
2. Sotgiu G, Gerli GA, Centanni S, Miozzo M, Canonica GW, Soriano JB, et al. Advanced forecasting of SARS-CoV-2 related deaths in Italy, Germany, Spain, and New York State. Allergy. 2020.
3. Corne JM, Marshall C, Smith S, Schreiber J, Sanderson G, Holgate ST, et al. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. Lancet. 2002;359(9309):831-4.
4. Jackson DJ, Trujillo-Torralbo MB, del-Rosario J, Bartlett NW, Edwards MR, Mallia P, et al. The influence of asthma control on the severity of virus-induced asthma exacerbations. J Allergy Clin Immunol. 2015;136(2):497-500 e3.
5. Sykes A, Edwards MR, Macintyre J, del Rosario A, Bakhsoliani E, Trujillo-Torralbo MB, et al. Rhinovirus 16-induced IFN-alpha and IFN-beta are deficient in bronchoalveolar lavage cells in asthmatic patients. J Allergy Clin Immunol. 2012;129(6):1506-14 e6.
6. Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med. 2005;201(6):937-47.
7. Contoli M, Message SD, Laza-Stanca V, Edwards MR, Wark PA, Bartlett NW, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. Nat Med. 2006;12(9):1023-6.
8. Zhang JJ, Cao YY, Dong X, Wang BC, Liao MY, Lin J, et al. Distinct characteristics of COVID-19 patients with initial rRT-PCR positive and negative results for SARS-CoV-2. Allergy. 2020.
9. Dong X, Cao YY, Lu XX, Zhang JJ, Du H, Yan YQ, et al. Eleven faces of coronavirus disease 2019. Allergy. 2020.
10. Novel Coronavirus Pneumonia Emergency Response Epidemiology T. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41(2):145-51.
11. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, et al. The impact of COPD and smoking history on the severity of Covid-19: A systemic review and meta-analysis. J Med Virol. 2020.
12. Ritchie AI, Singanayagam A. Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? Lancet. 2020.
13. Contoli M, Ito K, Padovani A, Poletti D, Marku B, Edwards MR, et al. Th2 cytokines impair innate immune responses to rhinovirus in respiratory epithelial cells. Allergy. 2015;70(8):910-20.
14. Brough HA, Kalayci O, Sediva A, Untersmayr E, Munblit D, Rodriquez Del Rio P, et al. Managing childhood allergies and immunodeficiencies during respiratory virus epidemics - the 2020 COVID-19 pandemic. Pediatr Allergy Immunol. 2020.
15. Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet. 2017;390(10095):659-68.
16. Gielen V, Johnston SL, Edwards MR. Azithromycin induces anti-viral responses in bronchial epithelial cells. Eur Respir J. 2010;36(3):646-54.
17. Porter JD, Watson J, Roberts LR, Gill SK, Groves H, Dhariwal J, et al. Identification of novel macrolides with antibacterial, anti-inflammatory and type I and III IFN-augmenting activity in airway epithelium. J Antimicrob Chemother. 2016;71(10):2767-81.
18. Bacharier LB, Guilbert TW, Mauger DT, Boehmer S, Beigelman A, Fitzpatrick AM, et al. Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses: A Randomized Clinical Trial. JAMA. 2015;314(19):2034-44.
19. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020:105949.