Letter to the Editor

Is there a place for anti-inflammatory therapy in COVID-19?

Wing Wai Yew[1], Kwok Chiu Chang[2], Denise P. Chan[1]

[1]Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong, Hong Kong, China; [2]Tuberculosis and Chest Service, Centre for Health Protection, Department of Health, Hong Kong, China

Correspondence to: Dr. Denise P. Chan. Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong, 2/F, Postgraduate Education Centre, Prince of Wales Hospital, Hong Kong, China. Email: denisechan@cuhk.edu.hk.

Submitted Jun 11, 2020. Accepted for publication Nov 02, 2020.
doi: 10.21037/jtd-20-2155
View this article at: http://dx.doi.org/10.21037/jtd-20-2155

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses substantial morbidity and mortality worldwide. Although the duration of viral shedding appears to be longer in patients with more severe COVID-19 (1), detailed study of viral dynamics has suggested the lack of correlation of viral load with clinical severity in some infected patients (2,3). In addition, the heterogeneity in the trend of viral load during therapy may pose difficulty for fully attributing the favourable outcome of patients to effective antiviral drugs. Accumulating clinical data and experimental evidence have suggested that host inflammatory response to most respiratory virus infections plays a substantial role in determining the clinical and pathological changes of these infections, on top of the direct cytological injury of the respiratory tract by the viruses (4-6). Pathological examination in fatal cases of COVID-19 has strongly suggested immune heightening with resultant host tissue damage. Thus it appears logical to contemplate ameliorating the apparently exaggerated host responses to eventuate a better patient outcome of the viral infection. We hereby humbly submit brief views regarding the modulation of inflammation in the management of new coronavirus infections.

A simplistic account of the immunopathogenesis underlying most respiratory infections, likely including that due to SARS-CoV-2, is as follows (4-8). Viral recognition by toll-like receptors, especially those present in macrophages and dendritic cells induce activation of antimicrobial innate immune response, principally involving NK cells and lymphocytes, with expression of type 1 interferons and other downstream signaling pathways. Respiratory virus infections can trigger oxidative stress, through induction of enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, in host cells, generating reactive oxygen species (ROS). Being microbiocidal, ROS helps activate innate immune response, but it can also damage host DNA, protein and lipid. In addition, macrophage mitochondrial ROS promotes pyroptosis, which is proinflammatory programmed cell death associated with inflammasome activation and release of proinflammatory cytokines such as interleukin (IL)-1β. Furthermore, there is concomitant disturbance of the balance between host antioxidant defence and inflammatory response, which are predominantly regulated by nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), respectively (8). Nrf2 is a key transcription factor that controls many aspects of cell homoeostasis in response to oxidative and toxic insults, including its mediation of basal and induced antioxidant proteins that clear ROS (8). NF-κB is a key family of transcription factors that mediate immune responses to bacterial and viral infections (8). Proinflammatory cytokines such as tumour necrosis factor (TNF)-α are among the most potent NF-κB activators, likely due to auto-amplification. It is observed that some respiratory virus infections, including that due to SARS-CoV-2, can be associated with substantial production of proinflammatory cytokines and chemokines such as TNF-α, IL-6, IL-8, C-C motif chemokine ligand 5 (CCL5, also known as RANTES) and C-X-C motif chemokine ligand 10 (CXCL10, also known as interferon gamma-induced protein 10, IP-10). Significantly high IL-6 levels were found in clinically severe COVID-19 patients with viraemia (9). Higher levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), IP-10, monocyte chemoattractant protein 1 (MCP-1), macrophage

inflammatory proteins (MIP)-1α and TNF-α were found in patients with COVID-19 requiring management in intensive care units compared to those who did not (10). Respiratory epithelial and endothelial cells interact with leukocytes, primarily mediated by cell adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1) and E-selectin (also known as endothelial-leukocyte adhesion molecule 1, ELAM-1). In concert with the cell-mediated immune response, oxidative stress significantly contributes to the overall host inflammatory responses. Furthermore, there may be a possibility of promotion of viral gene expression resulting from viral manipulation of NF-κB transcription factors (11), or a positive feedback loop regarding oxidative stress-inflammation and viral replication (12). Nrf2 overexpression, with putative link to antioxidant defence, has been shown to inhibit influenza virus replication (7). A delayed peaking in the viral load, observed in some clinically severe patients with COVID-19 (2), might be related to viral inhibition of type 1 interferons (5), or progressive worsening of oxidative stress-inflammation in their disease time-course. Oxidative stress might also increase the propensity for viral persistence resulting in a protracted disease course and sometimes increased mortality (13). Moreover, when host defence is compromised by the new coronavirus, inflammation of the respiratory tissue likely increases the risk of bacterial adherence/ invasion and secondary bacterial infections (14), thus further escalating host morbidity and mortality. Such background of immunopathogenesis possibly correlates well with the worse outcome of patients with diabetes mellitus or chronic cardiopulmonary diseases (15), as the oxidative stress and inflammation inherent to the comorbidity might compound that incurred by the new coronavirus. The mechanism is likely similar to that underlying the unfavourable outcomes of some tuberculosis patients with diabetes mellitus (16).

It is biologically plausible that anti-inflammatory therapy should be revisited or explored, although safe and efficacious vaccines and antiviral drugs are possibly the final answers to the control of the new coronavirus pandemic. Micronutrients such as vitamin C have known antioxidant and anti-inflammatory properties. Research is required to inform the role of micronutrients including vitamin C in the clinical management of COVID-19. Ambroxol has putative anti-inflammatory activity and has been shown to inhibit replication of influenza virus in the mouse model (17). Nonsteroidal anti-inflammatory drugs (NSAID) have antioxidant property of some degree and can inhibit the biosynthesis of a number of cytokines. While there exists reasonable evidence from observational studies of a link between NSAID and both respiratory and cardiovascular adverse effects (18), and the current evidence does not support routine use of antipyretics to treat fever in acute respiratory tract infection including COVID-19 (19), caution against regular NSAID use in patients with COVID-19 might be a good policy (18,20), except that COVID-19 patients regularly receiving NSAID for chronic inflammatory arthritis are recommended not to discontinue NSAID (21). Given the lack of evidence for or against the use of NSAID in COVID-19 (18,20,22-24), clinical trials are probably warranted to delineate the role of NSAID in the management of COVID-19. Recently, given the immunomodulatory and antiviral properties of the 4-aminoquinoline antimalarials, chloroquine and hydroxychloroquine, used alone or in combination with azithromycin, have been proposed as clinically useful in some patients with COVID-19 (25,26), but the therapeutic benefit has not been substantiated by robust randomized controlled trials (27). The National Institutes of Health have recommended against the use of chloroquine or hydroxychloroquine, or the use of hydroxychloroquine plus azithromycin, to treat COVID-19 (28). Despite a possibly controversial role regarding use of systemic corticosteroids in coronavirus infections based on benefit versus risk considerations (29-32), a recent randomized controlled trial has demonstrated that the use of dexamethasone in hospitalized COVID-19 patients resulted in lower 28-day mortality among those in need of either invasive mechanical ventilation or supplemental oxygen but not among those receiving no respiratory support (33). Inhaled corticosteroids appropriately administered might merit contemplation to explore its efficacy and safety. Interestingly there have been some anecdotal reports regarding its role in the management of tuberculous pyrexia (34). Some patients on long-term inhaled steroids appeared to be more protected against influenza pneumonia (35). There have been case reports regarding the usefulness of inhaled steroid in the treatment of bronchiolitis obliterates organising pneumonia (36), sometimes induced by viral infection. Given that viral infection including coronavirus is a major cause of exacerbation of chronic obstructive pulmonary disease and asthma, and inhaled steroids effectively reduces exacerbations, inhaled corticosteroids may reduce either the risk of viral infection or the inflammatory response that ensues (37). Recent reports have suggested that certain inhaled steroid congeners might inhibit the replication or

cytopathic activity of coronavirus including SARS-CoV-2 (38,39). A small case series of COVID-19 patients suggested therapeutic benefit from inhaled ciclesonide (40). Antiviral activity of recombinant interferon β-1a against SARS-CoV has been demonstrated *in vitro* (41). A recent randomized controlled trial suggested that interferon β-1b with ribavirin added to lopinavir-ritonavir within 7 days of symptom onset was superior to lopinavir-ritonavir in alleviating symptoms and shortening viral shedding in patients with COVID-19 (42), but without significant impact on oxygen use. It appears logical to harness the antiviral activity of type 1 interferons early to overcome initial immune evasion and avoid subsequent hyperinflammation resulting from immune cell infiltration and cytokine storms (5). Anti-cytokine therapy that blocks IL-1 or IL-6 signaling may help limit tissue damage from hyperinflammation secondary to excessive immune activation from cytokine storms (5,43), but there is still insufficient data to recommend use of IL-1 inhibitors or IL-6 inhibitors in patients with COVID-19 (28). After ascertaining the clinical usefulness of an anti-inflammatory agent, it is critically important to delineate the optimal dosage and timing of administration.

The available evidence pertaining to use of anti-inflammatory or immunomodulatory agents in COVID-19 only supports use of dexamethasone or alternative glucocorticoids in patients in need of mechanical ventilation or supplemental oxygen (28). It is much hoped that judicious use of anti-inflammatory therapy may help improve symptomatology and forestall disease progression in COVID-19.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was a free submission to the journal. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-2155). WWY was consultant to Otsuka Pharmaceutical Company until July 2016. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Zheng S, Fan J, Yu F, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. BMJ 2020;369:m1443.
2. Lui G, Ling L, Lai CK, et al. Viral dynamics of SARS-CoV-2 across a spectrum of disease severity in COVID-19. J Infect 2020;81:318-56.
3. Lescure FX, Bouadma L, Nguyen D, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis 2020;20:697-706.
4. Newton AH, Cardani A, Braciale TJ. The host immune response in respiratory virus infection: balancing virus clearance and immunopathology. Semin Immunopathol 2016;38:471-82.
5. Felsenstein S, Herbert JA, McNamara PS, et al. COVID-19: Immunology and treatment options. Clin Immunol 2020;215:108448.
6. Tay MZ, Poh CM, Rénia L, et al. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020;20:363-74.
7. Khomich OA, Kochetkov SN, Bartosch B, et al. Redox biology of respiratory viral infections. Viruses 2018;10:392.
8. Wardyn JD, Ponsford AH, Sanderson CM. Dissecting molecular cross-talk between Nrf2 and NF- B response pathways. Biochem Soc Trans 2015;43:621-6.
9. Chen X, Zhao B, Qu Y, et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. Clin Infect Dis 2020 Apr 17;ciaa449.
10. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.

11. Zhao J, He S, Minassian A, et al. Recent advances on viral manipulation of NF-κB signaling pathway. Curr Opin Virol 2015;15:103-11.
12. Hiscott J, Kwon H, Génin P. Hostile takeovers: viral appropriation of the NF-kB pathway. J Clin Invest 2001;107:143-51.
13. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
14. Hendaus MA, Jomha FA, Alhammadi AH. Virus-induced secondary bacterial infection: a concise review. Ther Clin Risk Manag 2015;11:1265-71.
15. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020;55:2000547.
16. Yew WW, Leung CC, Zhang Y. Oxidative stress and TB outcomes in patients with diabetes mellitus? J Antimicrob Chemother 2017;72:1552-5.
17. Yang B, Yao DF, Ohuchi M, et al. Ambroxol suppresses influenza-virus proliferation in the mouse airway by increasing antiviral factor levels. Eur Respir J 2002;19:952-8.
18. Little P. Non-steroidal anti-inflammatory drugs and covid-19. BMJ 2020;368:m1185.
19. Day M. Covid-19: European drugs agency to review safety of ibuprofen. BMJ 2020;368:m1168.
20. Capuano A, Scavone C, Racagni G, et al. NSAIDs in patients with viral infections, including Covid-19: Victims or perpetrators? Pharmacol Res 2020;157:104849.
21. Giollo A, Adami G, Gatti D, et al. Coronavirus disease 19 (Covid-19) and non-steroidal anti-inflammatory drugs (NSAID). Ann Rheum Dis 2020. [Epub ahead of print].
22. Rinott E, Kozer E, Shapira Y, et al. Ibuprofen use and clinical outcomes in COVID-19 patients. Clin Microbiol Infect 2020;26:1259.e5-7.
23. Moore N, Carleton B, Blin P, et al. Does ibuprofen worsen COVID-19? Drug Saf 2020;43:611–4.
24. Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? Ecancermedicalscience 2020;14:1023.
25. Devaux CA, Rolain JM, Colson P, et al. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents 2020;55:105938.
26. Gautret P, Lagier JC, Parola P, 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;56:105949.
27. Ferner RE, Aronson JK. Chloroquine and hydroxychloroquine in covid-19. BMJ 2020;369:m1432.
28. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. [Internet]. 2020 [cited 2020 Oct 2]. Available online: https://www.covid19treatmentguidelines.nih.gov/
29. Veronese N, Demurtas J, Yang L, et al. Use of corticosteroids in coronavirus disease 2019 Pneumonia: a systematic review of the literature. Front Med (Lausanne) 2020;7:170.
30. Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ 2020;192:E756-E767.
31. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395:473-5.
32. Shang L, Zhao J, Hu Y, et al. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet 2020;395:683-4.
33. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with COVID-19 - Preliminary report. N Engl J Med 2020. [Epub ahead of print].
34. Yew WW, Lee J, Chau CH. Role of inhaled budesonide in the treatment of tuberculous pyrexia. Chest 2000;118:567.
35. Malo de Molina, Aguilar M, Trisan A, et al. Inhaled corticosteroids and influenza A (H1N1) viral pneumonia. Eur Respir J [Internet]. 2012 [cited 2020 Oct 2];40(Suppl 56). Available online: https://erj.ersjournals.com/content/40/Suppl_56/P1916
36. Watson D, Fadem JJ. Bronchiolitis obliterans organizing pneumonia cured by standard dose inhaled triamcinolone: the first documented case. South Med J 1995;88:980-3.
37. Halpin DMG, Singh D, Hadfield RM. Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective. Eur Respir J 2020;55:2001009.
38. Matsuyama S, Kawase M, Nao N, et al. The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15. BioRxiv [Preprint]. 2020 [posted 2020 Mar 12; cited 2020 Oct 2]. Available online: https://www.biorxiv.org/content/10.1101/2020.03.11.987016v1
39. Jeon S, Ko M, Lee J, et al. Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved

drugs. Antimicrob Agents Chemother 2020;64:e00819-20.
40. Iwabuchi K, Yoshie K, Kurakami Y, et al. Therapeutic potential of ciclesonide inhalation for COVID-19 pneumonia: Report of three cases. J Infect Chemother 2020;26:625-32.
41. Hensley LE, Fritz LE, Jahrling PB, et al. Interferon-beta 1a and SARS coronavirus replication. Emerg Infect Dis 2004;10:317-9.
42. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 2020;395:1695-704.
43. Zhang C, Wu Z, Li JW, et al. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents 2020;55:105954.

Cite this article as: Yew WW, Chang KC, Chan DP. Is there a place for anti-inflammatory therapy in COVID-19? J Thorac Dis 2020;12(11):7076-7080. doi: 10.21037/jtd-20-2155