Received: 25 March 2020 | Accepted: 11 May 2020

DOI: 10.1111/ijcp.13535

PERSPECTIVE

INFECTIOUS DISEASES

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

Indomethacin and resveratrol as potential treatment adjuncts for SARS-CoV-2/COVID-19

Mark A. Marinella

Division of Hematology/Oncology, Wright State University School of Medicine, Dayton, OH, USA

Correspondence
Mark A. Marinella, 2300 Miami Valley Drive, Centerville, OH 45415, USA.
Email: Mmarinella@daytonphysicians.com

Abstract

The ongoing pandemic caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2, also known as COVID-19) has led to unprecedented challenges for the global healthcare system. This novel coronavirus disease phenotype ranges from asymptomatic carriage to fulminant cytokine storm with respiratory failure, polyorgan dysfunction and death. Severe disease is characterised by exuberant inflammation resulting from high circulating cytokines such as interleukin-6 and tumour necrosis factor. These inflammatory mediators are responsible for the detrimental effects on the immune, hematologic, respiratory, renal, gastrointestinal and other body systems. In addition to inhibition of viral replication, blunting this inflammatory response before overt cytokine storm is important to improve outcomes. Although there are upcoming promising agents such as remdesivir and convalescent plasma, inexpensive, safe and widely available adjunct treatments to ameliorate disease burden would be welcome. Two potential anti-inflammatory agents include indomethacin, which has been shown in experimental models to decrease canine coronavirus levels in dogs and exhibit antiviral activity against several other viruses and the polyphenol, resveratrol, a potent antioxidant that has shown antiviral activity against several viruses.

1 | INTRODUCTION

The rapid global spread of novel coronavirus, SARS-CoV-2, has resulted in unprecedented mobilisation of local and national governments, public health officials, paramedical personnel, basic scientists and clinicians, not only to treat patients, but also to thwart the spread of this efficient and virulent pathogen. In severe cases, SARS-CoV-2 induces liberation of cytokines and chemokines, such as interleukins (IL), interferons (IFN) and tumour necrosis factors (TNF), causing cytopathic effects as well as "cytokine" storm leading to organ failure[1]—a phenomena similar to overwhelming bacterial sepsis, which increases pro-inflammatory cytokines such as TNF and interleukin-6 (IL-6).[2] While it is vital to decrease viral basic reproductive potential (R0), it is also important to find specific therapies for this novel coronavirus, as treatment essentially is supportive in critically ill patients.[3] Convalescent plasma infusion, the antiviral, remdesivir and the immunomodulatory agents, chloroquine and hydroxychloroquine are among current therapeutic candidates for SARS-CoV-2, although there are cardiotoxicity concerns for chloroquine agents.[1,3] However, agents that are inexpensive, relatively nontoxic and readily available, which blunt the severity of established infection would be welcomed worldwide. Two potential agents include indomethacin and resveratrol.

2 | INDOMETHACIN

Indomethacin is an inexpensive, non-selective cyclooxygenase (COX) inhibitor that inhibits COX-1 and COX-2, and is used to treat a variety of inflammatory conditions. Indomethacin is a potent anti-inflammatory agent and inhibits COX enzymes more potently than aspirin.[4] Amici et al showed that indomethacin possesses antiviral

activity in vitro against severe acute respiratory syndrome coronavirus (SARS CoV) in monkey VERO cells as well as in vivo activity at relatively low doses (1 mg/kg) against canine coronavirus (CCoV) in dogs.[5] The authors concluded that indomethacin possesses direct antiviral activity for SARS CoV and CCoV by blocking viral RNA synthesis (>1000-fold reduction in virus yield in CCoV infected dogs), independent of anti-inflammatory effects.[5]

Several in vitro and in vivo studies in animals have also demonstrated varying degrees of antiviral activity of indomethacin. Indomethacin has been shown to interrupt the viral life cycle of various herpesviruses, and may diminish latent infections by inhibiting prostaglandin synthesis, which is blocked by indomethacin and other nonsteroidal drugs.[6] Ray et al demonstrated that COX-2 transcription increased after herpes simplex virus type I and pseudorabies virus infection of embryonic rat cells and that COX inhibitors decreased growth of the pseudorabies virus.[7,8] Cytomegalovirus induces accumulation of COX-2 and indomethacin decreased cell-to-cell spread of CMV in cultured fibroblasts in vitro.[9] Bahrami and colleagues reported that indomethacin 25 mg three times a day eradicated hepatitis B virus DNA in seven human patients.[10] Other studies have shown that indomethacin-induced inhibition of COX and antagonised mouse vesicular stomatitis virus encephalitis growth in vitro and in vivo.[11] As a final example, indomethacin reduced rotavirus infection in human intestinal Caco-2 cells, by inhibiting viral protein synthesis.[12] Although the activity of indomethacin in the above scenarios is mainly in vitro or in animal models, there is compelling data that indomethacin may be therapeutic in certain viral infections. Furthermore, this agent is available with predictable toxicity profiles and may be an option to consider in combatting human SARS-CoV-2.

Indomethacin, however, can induce side effects such as gastritis, renal dysfunction and platelet dysfunction,[4] that could be detrimental to patients with severe SARS-CoV-2 infection, especially if they have multiorgan dysfunction resulting from cytokine storm. Furthermore, some authors have reported that NSAIDS such as ibuprofen may be detrimental in patients with novel coronavirus, causing more severe infection or lead to later complications such as empyema, prolonged hospital stay or lung cavitation, as has been reported in patients with bacterial pneumonia.[13,14] However, the WHO recently did not recommend against ibuprofen use for infection with SARS-CoV-2.[15]

Studies have shown ibuprofen to decrease sputum IL-6 in cystic fibrosis patients[16] and synovial fluid IL-6 in patients with knee osteoarthritis,[17] which demonstrates that NSAIDS can lower IL-6 in human fluids. This lends biologic plausibility that COX inhibition with indomethacin could lower IL-6 levels in nasopharyngeal-respiratory tract secretions.

Whether using lower doses of indomethacin (eg, 25 mg three times daily) at first sign of infection (in outpatients after a positive nasopharynx swab) or for inpatients with adequate organ function and no evidence of cytokine storm is conjectural, but use of this agent along with gastric protective agents (eg, H2 blockers) may be prudent. Since cytokine storm is, at its root, an inflammatory response, well-timed blunting of this cascade with indomethacin could conceivably lower inflammatory mediators such as TNF and IL-6 as well as superoxide free radicals, which invoke cellular damage.[4]

Perhaps a clinical strategy would be to monitor IL-6 levels (or C-reactive protein [CRP] as a surrogate marker), upon admission in noncritical patients and start indomethacin when IL-6 (or CRP) begins to rise, and subsequently monitor levels daily. Indeed, well-timed anti-inflammatory agents such as NSAIDS and corticosteroids have been suggested to reduce systemic inflammation prior to the development of overwhelming systemic inflammation/cytokine storm.[18] Indomethacin could be used alone or more likely as an adjunct to antiviral therapy such as remdisivir in noncritical patients. It would be interesting to monitor time to clearance of the antigen from upper respiratory secretion, antibody kinetics and duration of symptomatic disease in patients treated with indomethacin. Given the cost and availability of this agent, indomethacin may warrant study in outpatients or admitted patients with documented infection with SARS-CoV-2 without evidence of cytokine storm.

3 | RESVERATROL

Resveratrol, a natural polyphenol compound found abundantly in grapes, red wine, mulberry and peanuts, possesses antioxidant, antitumour, antiviral and free radical scavenging properties.[19] Resveratrol belongs to the phytoalexin family of phytochemicals, which are antimicrobial-like compounds produced by plants in response to fungal infection or physiologic stress.[20] Resveratrol modulates inflammation response in a pleiotropic manner and scavenges free radicals such as superoxide, and may interfere with infections by altering numerous cellular pathways.[20,21]

Resveratrol has been reported to exhibit antiviral properties against a variety of viral pathogens in vitro and in vivo.[22] Lin et al demonstrated that resveratrol significantly inhibited Middle East Respiratory Syndrome Coronavirus (MERS-CoV) replication in vitro by inhibition of RNA production as well as other pleiotropic effects.[23] Resveratrol inhibited viral replication and mortality in ducklings infected with duck enteritis virus.[24] Zhao et al found that resveratrol was able to suppress pseudorabies virus (a herpesvirus affecting swine that causes fatal encephalitis as well as lung inflammation) in vitro by inhibiting intracellular viral multiplication.[25] Piglets inoculated with pseudorabies virus, who were supplemented with resveratrol at different dose levels for seven days prior to infection, had significantly lower viral loads than the untreated group as well as significantly decreased death rates (90% survival in the resveratrol group, with no deaths in the higher dosed groups—30 mg/kg and 10 mg/kg had 100% survival; the low dose group of 3 mg/kg had 90% survival).[25] Since resveratrol has limited oral bioavailability, some authors have suggested nanoparticle formulations or combination with modified *beta*-glucan in aqueous solutions may improve stability and absorption.[21,26] Intranasal resveratrol and carboxymethyl-*beta*-glucan mixture administered to infants decreased symptoms of the common cold.[26] As a final example of the biologic therapeutic plausibility for resveratrol for viral and/or SARS-CoV-2 infection, resveratrol

added to the diet of piglets for 21 days, decreased TNF-*alpha* levels and diminished diarrhoea because of rotavirus.[27] Although there are no data for using resveratrol in humans infected with SARS-CoV-2, the above studies demonstrate that this compound may be an adjunctive antiviral agent to consider, especially based on the data published by Linn et al showing activity against MERS-CoV in vitro.[23] Although dosing in humans is unknown, resveratrol is considered safe when taken at supplemental doses.

4 | CONCLUSION

Although randomised trial data are not yet available for indomethacin and resveratrol for treatment of or slowing progression of SARS-CoV-2 infection, these agents should be considered by the medical community as potentially worthy of further study as therapeutic adjuncts, given the relative safety, accessibility and low cost.

ORCID

Mark A. Marinella https://orcid.org/0000-0003-1335-9429

REFERENCES

1. Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak—an update on the status. *Mil Med Res*. 2020;7:11.
2. Marinella MA *Vibrio vulnificus Sepsis. Handbook of Cancer Emergencies*. Subdury, Mass: Jones and Bartlett Publishers. 2010;341-345.
3. Fauci AS, Lane HC, Redfield RR. Covid-19—navigating the uncharted. *N Engl J Med*. 2019;380 2185–2187.
4. Brunton LL, Parker L, Blumenthal DK, Buxton ILO. *Goodman and Gilman's Manual of Pharmacology and Therapeutics*. New York, NY: McGraw-Hill Medical; 2008:446-447.
5. Amici C, Di Caro A, Ciucci A, et al. Indomethacin has a potent antiviral activity against SARS coronavirus. *Antivir Ther*. 2006;11:1021-1030.
6. Reynolds AE, Enquist LW. Biological interactions between herpesviruses and cyclooxygenase enzymes. *Rev Med Virol*. 2006;16:393-403.
7. Ray N, Bisher ME, Enquist LW. Cyclooxygenase-1 and -2 are required for production of pseudorabies virus. *J Virol*. 2004;78:12964-12974.
8. Ray N, Enquist LW. Transcriptional response of a common permissive cell type to infection by two diverse alphaherpesviruses. *J Virol*. 2004;78:3489-3501.
9. Schroer J, Shenk T. Inhibition of cyclooxygenase activity blocks cell-to-cell spread of human cytomegalovirus. *Proc Natl Acad Sci USA*. 2008;105:19468-19473.
10. Bahrami H, Daryani NE, Haghpanah B, et al. Effects of indomethacin on viral replication markers in asymptomatic carriers of hepatitis B: a randomized placebo controlled trial. *Am J Gastroenterol*. 2005;100:856-861.
11. Chen N, Warner JL, Reiss CS. NSAID treatment suppresses VSV propagation in mouse CNS. *Virology*. 2000;276:44-51.
12. Rossen JW, Bouma J, Raatgeep RH, Büller HA, Einerhand AWC. Inhibition of cyclooxygenase activity reduces rotavirus infection at a postbinding step. *J Virol*. 2004;78:9721-9730.
13. Day M. Covid-19: ibuprofen should not be used for managing symptoms say doctors and scientists. *BMJ*. 2020;19:m1086.
14. Gupta R, Misra A. Contentious issues and evolving concepts in the clinical presentation and management of patients with COVID-19 infection with reference to use of therapeutic and other drugs used in co-morbid diseases (Hypertension, diabetes, etc.). *Diabetes Metab Syndr*. 2020;14:251-254.
15. Updated: WHO now doesn't recommend avoiding ibuprofen for COVID-19 symptoms. https://www.sciencealert.com/who-recommends-to-avoid-taking-ibuforfin-for-covid-19-symptoms
16. Chmiel JF, Konstan MW, Accurso FJ, et al. Use of ibuprofen to assess inflammatory biomarkers in induced sputum: implications for clinical trials in cystic fibrosis. *J Cyst Fibros*. 2015;14:720-726.
17. Gallelli L, Galasso O, Falcone E, et al. The effects of nonsteroidal anti-inflammatory drugs on clinical outcomes, synovial fluid cytokine concentration and signal transduction pathways in knee osteoarthritis. A randomized open label trial. *Osteoarthritis Cartilage*. 2013;21:1400-1408.
18. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. *Clin Immunol*. 2020;214:108393.
19. Marinella MA. *A summary of Selected Phytonutrient Dense Foods: Is There Data? Metronomic Phytonutrition: How Daily, Regular Intake of Plant-Based Foods May Decrease Cancer Risk*. Anchorage, AK: Beacon Publishing and Design; 2017:120.
20. Campagna M, Rivas C. Antiviral activity of resveratrol. *Biochem Soc Trans*. 2010;38:50-53.
21. Abba Y, Hassim H, Hamzah H, Noordin MM. Antiviral activity of resveratrol against human and animal viruses. *Adv Virol*. 2015; https://doi.org/10.1155/2015;18241
22. Zhao X, Tong W, Song X, et al. Antiviral effect of resveratrol in piglets infected with virulent pseudorabies virus. *Viruses*. 2018;10:457-467.
23. Lin SC, Ho CT, Chuo WH, Li S, Wang TT, Lin C-C. Effective inhibition of MERS-CoV infection by resveratrol. *BMC Infect Dis*. 2017;17:144-154.
24. Zhao X, Xu J, Song X, et al. Antiviral effect of resveratrol in ducklings infected with virulent duck enteritis virus. *Antiviral Res*. 2016;130:93-100.
25. Zhao X, Cui Q, Fu Q, et al. Antiviral properties of resveratrol against pseudorabies virus are associated with the inhibition of IkB kinase activation. *Sci Rep*. 2017;7:8772.
26. Baldassarre ME, Di Mauro A, Labellarte G, et al. Resveratrol plus carboxymethyl-beta-glucan in infants with common cold: a randomized double blind trial. *Heliyon*. 2020;6:e03814.
27. Cui Q, Fu Q, Zhao X, et al. Protective effects and immunomodulation on piglets infected with rotavirus following resveratrol supplementation. *PLoS One*. 2018;13:e0192692.

How to cite this article: Marinella MA. Indomethacin and resveratrol as potential treatment adjuncts for SARS-CoV-2/COVID-19. *Int J Clin Pract*. 2020;74:e13535. https://doi.org/10.1111/ijcp.13535