

Review Article

Role of poly (ADP) ribose polymerase-1 inhibition by nicotinamide as a possible additive treatment to modulate host immune response and prevention of cytokine storm in COVID-19

Mukul Arvind Gharote

Department of Medical Oncology, Mukta Cancer Clinic, Nashik, Maharashtra, India.



***Corresponding author:**

Dr. Mukul Arvind Gharote,
Department of Medical
Oncology, Mukta Cancer Clinic,
MF-70, MaghSector,
Sundarban Colony,
Near Deccan Petrol
Pump, Bhujbhal
Farm Road, Nashik,
Maharashtra, India.

mukul.gharote@gmail.com

Received : 31 March 2020

Accepted : 01 April 2020

Published : 30 April 2020

DOI

10.25259/IJMS_29_2020

Quick Response Code:



ABSTRACT

COVID-19 is rapidly spreading contagious disease spreading across the world. Patients at risk are elderly people and those with comorbidity. Early studies done on Chinese patients who suggest cytokine storm to be responsible for lung injury. We need to understand the mechanism of modulating such robust response of immunity and resultant cytokine storm. We suggest nicotinamide, a potential poly ADP ribose polymerase (PARP) inhibitor, as a supportive treatment for the prevention of cytokine storm from injuring the lung parenchyma. Nicotinamide supplementation albeit at high dose may modulate outcome in COVID-19. Nicotinamide was used previously to reduce ventilator-induced lung injury and lung injury due to hypoxia. Nicotinamide congeners are used to treat chronic lung disease like tuberculosis. Certainly, nicotinamide is effective pharmacotherapy in lung injury – whether acute or chronic. Other measures used in treating COVID-19 are focusing on targeting interleukin-6 – a cytokine responsible for mayhem, while few are targeting granulocyte-macrophage colony-stimulating factor. We suggest targeting PARP in addition to other measures to block cytokines. By inhibiting PARP course of COVID-19 may be altered. Understanding the pathophysiology of acute lung injury is crucial. PARP plays a pivotal role on cytokine release in response to any lung injury ranging from viral infection to hypoxia. Various antiviral defenses and immune response need to be studied in detail.

Keywords: COVID-19, Poly ADP ribose polymerase-1 inhibition, Interleukin-6, Nicotinamide, SARS-CoV-2

INTRODUCTION

Dendritic cell (DC) potency is the key to viral defense mechanism as they are the antigen presenting cells. These APCs help in boosting host defenses against the viral infection. DCs provide a first line of defense following influenza virus A infection. I can detect viral products; DCs alert the immune system to the presence of infectious virus.^[1] There are mainly four types of DCs in our body.^[2]

- Type 1 and Type 2 – conventional antigen presenting cells to T lymphocytes
- Plasmacytoid DC – major IFN-1 producers
- Monocyte-derived DC – produce inflammatory cytokines.

After inoculation of virus, during mucosal inflammation, the first DC exposed is monocyte-derived DC. However, the one responsible for cytokine and pro-inflammatory response to viral infection

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

©2019 Published by Scientific Scholar on behalf of Indian Journal of Medical Sciences

is plasmacytoid DC. It is also supposed to be the reason behind aggressive disease course in dengue and other viral infections.^[3] Human SARS-CoV-2 virus causing COVID-19 also leads to dreaded course due to cytokine storm in lung tissue, leading to fatality.^[4] Intervention to inhibit such cytokine storm from being generated can prevent cases from fatal outcome. Worldwide, deaths due to COVID-19 are increasing day by day. Measures to curb these deaths are underway with no obvious benefits. Patients at risk are the elderly and those with comorbid illness such as diabetes, hypertension, chronic airway diseases, and cancers.

Inhibition of the cytokine storm may prevent the emergence of fatal lung injury, as observed in many case reports, the cytokine milieu was higher in patients, landing in ICU as compared to non-intensive care unit patients. The recruitment of cytokine in the cytokine storm that results in fatal disease is similar to the activation of airway epithelial cells immune response. Airway epithelial response to viral infection is release of various cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), granulocyte colony-stimulating factor (CSF), and granulocyte-macrophage-CSF (GM-CSF).^[5] High IL-6 levels are associated with disease severity, but ablation of IL-6 signaling, by IL-6 receptor antibodies, can lead to uncontrolled virus replication resulting in greater mortality.^[6] TNF- α , on the other hand, leads to impair viral replication, enhances cytotoxic activity and cytokine production by leukocytes, and activates endothelial cells.^[7] Elevated levels of TNF- α have been associated with greater morbidity during infection with highly pathogenic virus, and blocking activity of TNF- α attenuates immune-mediated pathology.

GM-CSF is elevated in COVID-19,^[8] GM-CSF leads to the activation of DCs and macrophages. Which in other case should have recruited macrophages to clear viral-infected cells by phagocytosis? But that seems to be have been overwhelmed by immune-mediated injury to lung and mortality due to cytokine storm.^[5]

One thing is crystal clear that fatal course of COVID-19 is the result of mature immune response and resultant cytokine storm, leading to fatal lung injury. Hence, children have mild/moderate disease, but it is the elderly who are at risk.

MEASURES TO CURB CYTOKINE STORM

Worldwide focus is on targeting IL-6, tocilizumab-IL-6 receptor humanized antibody has shown promising result in dealing with COVID-19 patients. It was previously used to treat rheumatoid arthritis.

Other studies are focusing on targeting GM-CSF. However, all these measures also put at the risk of increased viral replication.^[6] Such measures can potentially cause more

morbid outcome or prolonged course of disease. It may also lead to increased community transmission.

NICOTINAMIDE IN INFLAMMATORY LUNG INJURY

Nicotinamide leads to the inhibition of poly ADP ribose polymerase (PARP) activity. This, in turn, inhibits inducible nitric oxide synthase expression, reduced free radicals and pro-inflammatory cytokines with restoration of adenosine triphosphate.^[9] Nicotinamide is also used to mitigate acute lung injury due to bleomycin.^[10] Nicotinamide and its structurally similar isoniazid, pyrazinamide are used to treat tuberculosis, nicotinamide is used in treating HIV.^[11] In cases of COVID-19 infection and resultant cytokine storm, leading to acute lung injury, if we focus on restoration of ATP by nicotinamide supplementation, this approach may mitigate inflammatory response and ultimately outcome.

Elderly population is otherwise deficient in niacin, putting them at increased risk of tissue injury due to COVID-19 and poor recovery of tissue damage. Niacin supplementation will help them in restoring tissue damage.^[12] It may result in better outcome. Aging leads to slower metabolism and reduced absorption of dietary niacin.

NICOTINAMIDE SUPPLEMENTATION MAY HELP COMBAT COVID-19

Targeting cytokine storm is what everyone targeting and it seems apt, but if we think of tissue restoration and prevention of damage due to cytokine storm, then supplementation of key factors needed for mitigating tissue injury should be taken into consideration. Niacin supplementation has shown reduction in pro-inflammatory cytokines although in animal model.^[13]

In vitro studies done on endotoxemia due to lipopolysaccharide, i.e., outer membrane of Gram-negative bacteria, known for inducing cytokine storm due to cytokine activation through aberrant pathway, leading to sepsis, were reduced by nicotinamide supplementation in a dose-dependent manner.^[14]

A systematic review of such supplementation suggested that Vitamin B deficiency may weaken host immune response; they should be supplemented to the virus-infected patients to enhance their immune system. Therefore, B vitamins could be chosen as a basic option for the treatment of COVID-19.^[15]

This systematic review also suggested role of Vitamin B3 (nicotinamide) as of potential use. Vitamin B3 treatment significantly inhibited neutrophil infiltration into lungs and produced strong anti-inflammatory effect during ventilator-induced lung injury (VILI).^[15] In one study done on mice, nicotinamide was associated with hypoxemia in VILI, but

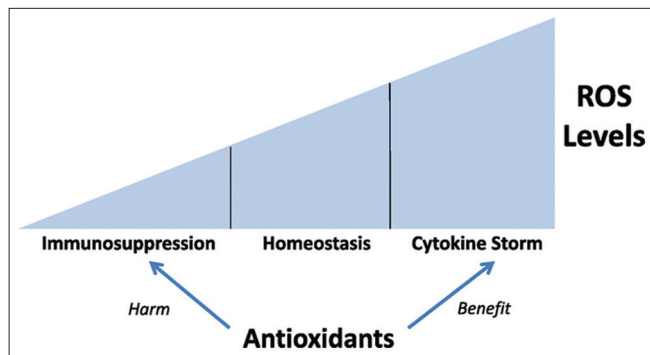


Figure 1: A perfect balance between Antioxidants and level of Reactive oxygen species, decides the outcome between immunosuppression and Cytokine storm.^[24]

even they mentioned that neutrophil-induced lung injury was reduced due to niacin supplementation.^[16]

ROLE OF PARP INHIBITION IN ACUTE LUNG INJURY

PARP plays an important role in the immune response of lung.^[17] PARP-1 inhibitor decreased the levels of IL-6 and active plasminogen activator inhibitor 1 in the lungs, attenuated leukocyte lung transmigration, and reduced pulmonary edema and apoptosis.^[18] PARP is known to have pathogenesis in mechanical VILI.^[19]

TARGETING PARP IN COVID-19 – CAN IT BE USED FOR MASS PROHYLAXIS?

Considering the molecular mechanism of COVID-19 targeting PARP is a sensible approach, out of which nicotinamide can be economical way to deal with PARP inhibition. PARP inhibitors can be repurposed in acute lung injury.^[20] PARP inhibitors in clinical development mimic the nicotinamide moiety of nicotinamide adenine dinucleotide. Hence, nicotinamide, which is the first PARP inhibitor, has activity against PARP-1, PARP-2 can be used as PARP inhibitor.^[21]

The body's niacin requirement is met not only by nicotinic acid and nicotinamide present in the diet but also by conversion from the dietary protein-containing tryptophan. The relative contribution of tryptophan is estimated as follows: 60 mg of tryptophan = 1 mg of niacin = 1 mg of niacin equivalents.^[22] Nicotinamide recommended daily allowance is 0.3 mg/kg/day as recommended daily allowance. However, the dose needed for PARP inhibition is between 300 and 500 mg/kg. It is a very high dose of nicotinamide. Adverse effects of nicotinamide are rare and have occurred mainly with high oral doses (≥ 6 g/day), which include nausea, vomiting, liver toxicity, headache, fatigue, and dizziness.^[23]

We must also know that dealing with immunity, one must be sure of timing of the administration of antioxidant to

modulate immunity as suppression. Following figure may explain it in better way.

ROLE OF ANTIOXIDANT SUPPLEMENTATION

Reactive oxygen species (ROS) levels decide immune responses. The levels of ROS lead to the physiological responses of inflammatory cells. High levels of intracellular ROS levels result in exaggerated inflammatory responses associated with cytokine storm, and relatively low ROS levels give hypoinflammatory response, leading to immunosuppression. ROS levels in the intermediate range result in normal immune cell function.

The use of antioxidants may only be beneficial during periods of exaggerated inflammatory responses but may be detrimental during periods of relative immunosuppression. Thus, the efficacy of antioxidants is dependent on an individual's inflammatory response profile with timing and duration of antioxidant administration critical to demonstrating a salutary effect. As a therapeutic intervention, individualizing dosing will likely be a crucial element in optimizing the potential of an antioxidant strategy.^[24]

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Waithman J, Mintern JD. Dendritic cells and influenza A virus infection. *Virulence* 2012;3:603-8.
2. Sesti-Costa R, de Moraes-Vieira PM, Cervantes-Barragan L. Dendritic cells: Immune response in infectious diseases and autoimmunity. *Mediators Inflamm* 2020;2020:294852.
3. Ho LJ, Wang JJ, Shaio MF, Kao CL, Chang DM, Han SW, *et al.* Infection of human dendritic cells by dengue virus causes cell maturation and cytokine production. *J Immunol* 2001;166:1499-506.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497-506.
5. 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.
6. Teijaro JR. The role of cytokine responses during influenza virus pathogenesis and potential therapeutic options. *Curr Top Microbiol Immunol* 2015;386:3-22.

7. Horiuchi T, Mitoma H, Harashima SI, Tsukamoto H, Shimoda T. Transmembrane TNF-alpha: Structure, function and interaction with anti-TNF agents. *Rheumatology (Oxford)* 2010;49:1215-28.
8. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, *et al.* Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *Natl Sci Rev* 2020. doi: 10.1093/nsr/nwaa041.
9. Su CF, Liu DD, Kao SJ, Chen HI. Nicotinamide abrogates acute lung injury caused by ischaemia/reperfusion. *Eur Respir J* 2007;30:199-204.
10. Nagai A, Matsumiya H, Hayashi M, Yasui S, Okamoto H, Konno K. Effects of nicotinamide and niacin on bleomycin-induced acute injury and subsequent fibrosis in hamster lungs. *Exp Lung Res* 1994;20:263-81.
11. Abrams B, Duncan D, Hertz-Picciotto I. A prospective study of dietary intake and acquired immune deficiency syndrome in HIV-seropositive homosexual men. *J Acquir Immune Defic Syndr (1988)* 1993;6:949-58.
12. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, *et al.* COVID-19 infection: The perspectives on immune responses. *Cell Death Differ* 2020. doi: 10.1038/s41418-020-0530-3.
13. Lipszyc PS, Cremaschi GA, Zorrilla-Zubilete M, Aón Bertolino ML, Capani F, Genaro AM, *et al.* Niacin modulates pro-inflammatory cytokine secretion. A potential mechanism involved in its anti-atherosclerotic effect. *Open Cardiovasc Med J* 2013;7:90-8.
14. Ungerstedt JS, Blömbäck M, Söderström T. Nicotinamide is a potent inhibitor of proinflammatory cytokines. *Clin Exp Immunol* 2003;131:48-52.
15. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. *J Med Virol* 2020;92:479-90.
16. Jones HD, Yoo J, Crother TR, Kyme P, Ben-Shlomo A, Khalafi R, *et al.* Nicotinamide exacerbates hypoxemia in ventilator-induced lung injury independent of neutrophil infiltration. *PLoS One* 2015;10:e0128735.
17. Legutko A, Lekeux P, Bureau F. NAD+-consuming enzymes in the regulation of lung immune responses. *Open Immunol J* 2009;2:42-51.
18. Vaschetto R, Kuiper JW, Chiang SR, Haitsma JJ, Juco JW, Uhlig S, *et al.* Inhibition of poly (adenosine diphosphate-ribose) polymerase attenuates ventilator-induced lung injury. *Anesthesiology* 2008;108:261-8.
19. Kummar S, Chen A, Parchment RE, Kinders RJ, Ji J, Tomaszewski JE, *et al.* Advances in using PARP inhibitors to treat cancer. *BMC Med* 2012;10:25.
20. Kim JH, Suk MH, Yoon DW, Kim HY, Jung KH, Kang EH, *et al.* Inflammatory and transcriptional roles of poly (ADP-ribose) polymerase in ventilator-induced lung injury. *Crit Care* 2008;12:R108.
21. Kouhpayeh S, Shariati L, Boshtam M, Rahimmanesh I, Mirian M, Zeinalian M, *et al.* The molecular story of COVID-19; NAD+ depletion addresses all questions in this infection. 2020;2020:2020030346.
22. Horwitt MK, Harper AE, Henderson LM. Niacin-tryptophan relationships for evaluating niacin equivalents. *Am J Clin Nutr* 1981;34:423-7.
23. Kaanders JH, Stratford MR, Liefers J, Dennis MF, van der Kogel AJ, van Daal WA, *et al.* Administration of nicotinamide during a five- to seven-week course of radiotherapy: Pharmacokinetics, tolerance, and compliance. *Radiother Oncol* 1997;43:67-73.
24. Jain M, Chandel NS. Rethinking antioxidants in the intensive care unit. *Am J Respir Crit Care Med* 2013;188:1283-5.

How to cite this article: Gharote MA. Role of poly (ADP) ribose polymerase-1 inhibition by nicotinamide as a possible additive treatment to modulate host immune response and prevention of cytokine storm in COVID-19. *Indian J Med Sci* 2020;72(1):25-8.