

Therapeutic Strategies with Synbiotics, Thalidomide, and Celecoxib for Severe COVID-19 Pneumonia

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June 11, 2020

Abstract

Dysregulation of proinflammatory cytokines promotes immune-mediated injuries. Epithelial-cell proliferation and an increase in lung macrophages have both been associated with the 2003 SARS-CoV infection. Proinflammatory cytokines as well as lipopolysaccharide and pathogen-associated molecular patterns (PAMPs) promote macrophage transition which promotes ongoing inflammation. PAMPs are primarily sensed by Toll-like receptors and/or by angiotensin-converting enzyme 2; this interaction serves to activate NF- κ B to promotes synthesis and secretion of proinflammatory cytokines. Activated immune cells secrete large amounts of specific proinflammatory cytokines including IL-1, IL-6, IL-8, TNF- α , and TGF- β 1 which can promote severe lung injury. As such, immunomodulatory drugs alone may have an impact on the cytokine storm even without the addition of antiviral agents. The central transcription factor, NF- κ B, induces angiogenesis during cancer progression; combinations of pharmacological agents, including thalidomide and celecoxib, show promising results in cancer treatment studies. This may be due to a low-level, chronic cytokine storm similar to that described for acute and chronic hepatitis as well as for cirrhosis and hepatoma. As previously described, I have used thalidomide, celecoxib, and low dose cytotoxic agents since 2000 for the successful treatment of a variety of cancers. This regimen is cited or introduced in leading medical journals. Thalidomide is an immunomodulatory agent that modulates the activities of NF- κ B in combination with the cyclooxygenase-2 inhibitor, celecoxib. The combination of thalidomide and celecoxib might limit the inflammatory symptoms when used to treat severe COVID-19 pneumonia due to infection with SARS-CoV-2.

Clinical Review

Therapeutic Strategies with Synbiotics, Thalidomide, and Celecoxib for Severe COVID-19 Pneumonia

Short title: Treatment for severe COVID-19 pneumonia

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Key words: proinflammatory cytokines, macrophages, SARS-CoV, thalidomide, celecoxib

Abbreviations used in this paper:

PAMP: pathogen-associated molecular pattern
 PRRs: pattern-recognition receptors
 TLR: Toll-like receptor
 SARS: severe acute respiratory syndrome
 MERS: Middle East respiratory syndrome
 NF- κ B: nuclear factor kappa B
 IL: interleukin
 TNF- α : tumor necrosis factor- α
 TGF- β : Transforming growth factor- β
 SARS-CoV: severe acute respiratory syndrome coronavirus
 MERS-CoV: Middle East respiratory syndrome coronavirus
 COVID-19: 2019 novel coronavirus
 ACE2: angiotensin-converting enzyme 2
 MyD88: myeloid differentiation factor 88
 COX-2: cyclooxygenase-2
 AMPK: AMP-activated protein kinase
 VEGF: VEGF
 bFGF: basic fibroblast growth factor
 MCP-1: monocyte chemoattractant protein-1
 iNOS: inducible nitric oxide synthase

Summary

Dysregulation of proinflammatory cytokines promotes immune-mediated injuries. Epithelial-cell proliferation and an increase in lung macrophages have both been associated with the 2003 SARS-CoV infection. Proinflammatory cytokines as well as lipopolysaccharide and pathogen-associated molecular patterns (PAMPs) promote macrophage transition which promotes ongoing inflammation. PAMPs are primarily sensed by Toll-like receptors and/or by angiotensin-converting enzyme 2; this interaction serves to activate NF- κ B to promotes synthesis and secretion of proinflammatory cytokines. Activated immune cells secrete large amounts of specific proinflammatory cytokines including IL-1, IL-6, IL-8, TNF- α , and TGF- β 1 which can promote severe lung injury. As such, immunomodulatory drugs alone may have an impact on the cytokine storm even without the addition of antiviral agents. The central transcription factor, NF- κ B, induces angiogenesis during cancer progression; combinations of pharmacological agents, including thalidomide and celecoxib, show promising results in cancer treatment studies. This may be due to a low-level, chronic cytokine storm similar to that described for acute and chronic hepatitis as well as for cirrhosis and hepatoma. As previously described, I have used thalidomide, celecoxib, and low dose cytotoxic agents since 2000 for the successful treatment of a variety of cancers. This regimen is cited or introduced in leading medical journals. Thalidomide is an immunomodulatory agent that modulates the activities of NF- κ B in combination with the cyclooxygenase-2 inhibitor, celecoxib. The combination of thalidomide and celecoxib might limit the inflammatory symptoms when used to treat severe COVID-19 pneumonia due to infection with SARS-CoV-2.

Introduction

Coronavirus infection is typically associated with mild clinical symptoms, save for those due to infection with severe acute respiratory syndrome coronavirus (SARS-CoV)¹, the Middle East respiratory syndrome coronavirus (MERS-CoV)^{2, 3}, and most recently, with SARS-CoV-2. An understanding of the pathophysiology of SARS-CoV-associated pneumonia induced will be helpful toward understanding the disease associated with the novel SARS-CoV-2 pathogen, a severe pneumonia known as Coronavirus Disease 2019 (2019-nCoV or COVID-19). Most of the published reports indicate that fatal COVID-19 has a clinical presentation that resembles that due to the original 2003 SARS-CoV pathogen. Most notably, in both cases, synthesis and release of proinflammatory cytokines has been associated with disease severity. Ongoing production can result in a cytokine storm and acute respiratory distress syndrome which are findings that can lead to fatal disease⁴. Toll-like receptors (TLRs), NF- κ B, macrophages, and proinflammatory cytokines were all found to be involved in the development of severe pneumonia⁵.

Toll-like Receptor Family

As in the case of SARS-CoV, angiotensin-converting enzyme 2 (ACE2) has been identified as main host cell receptor of SARS-CoV-2⁶. The ACE2 receptor was detected on cells from various human organs including lung alveolar epithelial cells and enterocytes of the small intestine. Interestingly, virus-activation of ACE2 can promote signaling and activation of NF- κ B similar to that mediated by the TLRs^{7,8}.

TLRs also play important roles with respect to the outcome of viral infection. TLRs play a central role in promoting innate immune responses via their interactions with PAMPs as pattern-recognition receptors (PRRs) both at the plasma membrane and within endosomes. Downstream signaling pathways of TLRs result in the activation of nuclear factor kappa B (NF- κ B)⁵ mainly via signals transmitted through myeloid differentiation factor 88 (MyD88)^{9, 10, 11, 12}. Other factors involved in TLRs-mediated modulation of NF- κ B are endosomal acidification¹³; activation of this pathway results in the production of proinflammatory cytokines and type I interferons. TLRs have been identified on B-lymphocytes, NK cells, dendritic cells, and macrophages, as well as on non-immune cells, including fibroblasts, epithelial cells and endothelial cells^{14, 15}. TLR3 may play a critical role in detecting RNA viruses and altering the pathogenesis of acute virus infection. Activation of this pathway may result in damage to alveolar and bronchial epithelial cells, as well as in various immune cells such as macrophages¹⁶. Bronchial epithelial cells and alveolar cells of lower respiratory tract express increasing amounts of TLR4 in response to inflammatory cell infiltration observed in response to coronavirus and other virus infections^{11, 17}. All TLR signaling pathways result in the activation NF- κ B which is the master regulator of inflammatory cytokine expression⁵.

Πολε οφ ΝΦ- κ B

As there are no vaccines or conventional drugs available for the treatment of SARS-CoV-2, we might consider the possibility of using drugs that can suppress NF- κ B and thereby limit the inflammatory response to the virus pathogen^{18, 19}. NF- κ B is a ubiquitous and pleiotropic protein that regulate more than 400 genes associated with the immune responses including inflammation, immunity, cell proliferation, differentiation, and survival^{20, 21}.

The canonical and non-canonical NF- κ B signaling pathways differ with respect to downstream signaling involved in stress responses and for the regulation of cell proliferation and apoptosis; this provides a means for effective orchestration of inflammatory and immune responses²² and to modulate a number of different disorders including the inflammatory basis of metabolic diseases, glycolysis, and oxidative metabolism²³. Therefore, NF- κ B could be a major target for therapeutic intervention²⁴.

Virus-induced NF- κ B activity can promote or suppress viral activity^{24, 25, 26}. The initial immune response to viral infections includes the induction of numerous cytokines; TNF- α and IL-1 β play key roles in the early induction of inflammation and innate immune responses²⁷. Viral infections are controlled directly by TNF- α . Moreover, these cytokines induce the synthesis and release of additional cytokines, promote the expression of cell adhesion molecules, and enhance the innate cytotoxicity of macrophages and neutrophils²⁸. Moreover, activated NF- κ B cause cytokine storm²⁹.

Inflammatory Cytokines and Alveolar Epithelium

The bronchial epithelium is a primary target for respiratory viruses²⁸. Alveolar epithelium plays an important role in promoting cell barrier functions and strengthening cell-cell junctions against virus-induced disruption of tight junctions. However, virus infected epithelial cells express cytokines that primarily attract macrophages. Once recruited, the activated macrophages promote activation of adjacent endothelial cells. Infiltrating macrophages produce reactive oxygen species and nitric oxide³⁰ that serve to damage the barrier³¹. Macrophages also promote epithelial-cell apoptosis epithelial cells and mediate phagocytosis of apoptotic cells^{31, 32, 33}.

Synbiosis and Berberine

Microbes in the gut play a central role in modulating immune responses, inflammation, and angiogenesis³¹. Microbial dysbiosis is an underlying factor in a variety of human disorders including metabolic diseases (obesity, type 2 diabetes mellitus), respiratory tract infections, appendicitis, and cardiovascular diseases³⁴. The Gram-negative periodontal pathogen, *Fusobacterium nucleatum* plays an important role in promoting dysbiosis³⁵. Alkalinized stomach contents due to *Helicobacter pylori* facilitate passage of microbes; likewise, cigarette smoking³⁶ promotes the proliferation of anaerobic *F. nucleatum* which stimulates cells to produce proinflammatory cytokines, including IL-6, IL-8, and TNF α through TLRs³⁷.

The actions of proinflammatory cytokines promote hypoxia, which results in the release HIF-1 that induces angiogenesis. Hypoxia itself leads to the production of proinflammatory cytokines via the NF- κ B /COX-2 pathway and thereby exacerbates local inflammatory conditions³⁸.

Patients with underlying disorders that are caused by or related to dysbiosis are more susceptible to COVID-19, as they are primed to exacerbate the cytokine storm produced by both dysbiosis and virus infection⁷. Therefore, I suggest that synbiotics might be combined with thalidomide and celecoxib to generate an effective therapeutic regimen.

The combination of thalidomide and celecoxib is important as it will serve to suppresses the production of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and COX-2, the three key mediators of angiogenesis³⁹.

Synbiosis promoted by berberine will serve to limit the production of proinflammatory cytokines and promote the secretion of short chain fatty acids that are beneficial toward positive systemic immunomodulation. Berberine is an isoquinoline alkaloid purified from Japanese herb, *Phellodendron amurense* (known as KI-HADA in Japanese) that is used for the treatment of microbe-associated diarrhea⁴⁰. The anti-inflammatory activity of berberine involves activation of AMP-activated protein kinase (AMPK)⁴¹ and inhibition of NF- κ B and AP-1 signaling pathways⁴². Berberine-mediated inhibition of these pathways limits both inflammation and carcinogenesis due to down-regulation of cytokines and proinflammatory enzymes, including TNF- α , IL-1 β , IL-6, monocyte chemoattractant protein-1 (MCP-1), inducible nitric oxide synthase (iNOS), and COX-2^{43, 44}. Patients with obesity, type 2 diabetes mellitus, hypertension, and/or a past history of acute appendicitis or *H. pylori* infection must be carefully observed while under this regimen.

Treatment

At present, there is no evidence from randomized controlled trials that supports the use of any specific drug regimen in patients with COVID-19. However, as I indicate here, there exist important common modalities that link the virus-induced cytokine storm to malignancies, notably, both conditions result in overexpression of proinflammatory cytokines and angiogenesis factors via the activation of NF- κ B²⁴.

Synbiotics

Notably among mild COVID-19 patients, it will be important to maintain a healthy immune response with a favorable balance of intestinal microbes by introducing synbiotics which will address any issues associated with dysbiosis in the gastrointestinal tract of the host. The mechanism of action of synbiotics suggests that

supplementation acts to promote probiotic-mediated reductions in NF- κ B activation and TNF- α production; in these cases, synbiotics function as immunomodulatory agents^{45, 46}.

Berberine

Berberine can contribute to the maintenance of healthy gut homeostasis together with probiotics and prebiotics⁴⁷. Berberine is poorly water soluble and has low bioavailability; as such, it promotes few adverse events when introduced to the gut^{48, 49 50}.

Thalidomide

Thalidomide suppresses activated NF- κ B that drives malignant cell proliferation, inflammation, angiogenesis, and poorly-regulated immune responses.^{51,52,53,54} Thalidomide also has an immunomodulatory effect when introduced together with the COX-2 inhibitor, celecoxib; together, these agents suppress the production of proinflammatory cytokines such as TNF- α and interleukin-8⁵⁵ through inhibition of NF- κ B by inhibiting the activity of the I κ B kinase⁵⁶. Thalidomide may be a powerful drug for the treatment of severe COVID-19 pneumonia. Patients undergoing treatment with thalidomide must be under the careful supervision of the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program⁵⁷.

Celecoxib

COX-2 is constitutively overexpressed in association with acute and chronic inflammation and also in malignant tumors⁵⁸. Inflammation induced by pathogens and in response to disordered metabolic states such as obesity is associated with expression of COX-2⁵⁹. Prostaglandin and proinflammatory cytokine production is limited by COX-2 which results in a down-regulation of the cytokine storm⁶⁰ and angiogenesis^{61,62,63}. It is reported that celecoxib modulates I κ B α degradation and phosphorylation and suppresses IKK activity in a dose-dependent manner⁶⁴.

Conclusion

In conclusion, the combination of thalidomide and celecoxib together with an effort to maintain symbiosis with berberine are all important factors that may help mitigate the SARS-CoV-2-induced cytokine storm. In mild cases, one can focus on maintaining a healthy immune response via the administration of synbiotics. In moderate-to-severe cases, immunomodulatory agents and synbiotics, including berberine, may help to prevent the lethal cytokine storm⁶⁰.

1. Thalidomide and Celecoxib

Low molecular weight immunomodulatory agents (<350 Da) can cross the cell membrane and limit activation of NF- κ B.

Thalidomide (200 mg/day), Celecoxib (400 mg/day)

2. Symbiotics and Berberine

Function by down-regulating proinflammatory cytokines

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interests: None

Ethics Approval: This is Review article - Ethics committee approval and informed consent are not needed.

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