



REVIEW



Exploring NF κ B pathway as a potent strategy to mitigate COVID-19 severe morbidity and mortality

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Abstract

The pandemic of coronavirus disease 2019 (COVID-19), for which there does not appear to be an approved cure, the primary treatment options consist of non-pharmacological preventive measures and supportive treatment that are aimed at halting the progression of the disease. Nuclear factor kappa B (NF κ B) presents a promising therapeutic opportunity to mitigate COVID-19-induced cytokine storm and reduce the risk of severe morbidity and mortality resulting from the disease. However, the effective clinical application of NF κ B modulators in COVID-19 is hampered by a number of factors that must be taken into consideration.

This paper therefore explored the modulation of the NFB pathway as a potential strategy to mitigate the severe morbidity and mortality caused by COVID-19. The paper also discusses the factors that form the barrier, and it offers potential solutions to the various limitations that may impede the clinical use of NF κ B modulators against COVID-19.

This paper revealed and identified three key potential solutions for the future clinical use of NF κ B modulators against COVID-19. These solutions are pulmonary tissue-specific NF κ B blockade, agents that target common regulatory proteins of both canonical and non-canonical NF κ B pathways, and monitoring clinical indicators of hyperinflammation and cytokine storm in COVID-19 prior to using NF κ B modulators.

Keywords: COVID-19, SARS-CoV-2, NF κ B, cytokine storm.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic, the current unfolding primary disease of respiratory system that occurs due to infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogen and resulting in acute respiratory distress syndrome (ARDS), remains a plague that poses greatest global challenge to every aspect of humans' life with no definite end in sight as therapeutic cure at the moment.^{1,2} The clinical manifestation of COVID-19 variably range from asymptomatic to severe cases, with severity associated with lethal and life threatening consequences such as intense pneumonia, ARDS, respiratory failure, septic shock, multiple organ failure and mortality.^{3,4}

There are three main factors that made COVID-19 a challenging and dreadful disease; first is the absence of definitive cure;⁵⁻⁷ secondly the high infection rate of COVID-19 ascribed to SARS-CoV-2 increased affinity for ACE2 cognate receptor relative to other coronaviruses that cause lower respiratory tract infections;⁸ third is the severe morbidity and mortality due to the disease attributed to cytokine storm.^{9,10} The hallmark of cytokine storm in COVID-19 is aberrant and excessive generation of pro-inflammatory cytokines due to loss of regulatory control mechanism in the host immune response to SARS-CoV-2 infection.¹¹ Pulmonary host immune cells generate an increase in pro-inflammatory cytokine production necessary to coordinate immune response to SARS-CoV-2 virus. Ideally, after generation of these cytokines and elimination of the virus, homeostasis regulatory mechanisms are activated aimed at returning the immune cells to basal state through generation of anti-inflammatory cytokines and host tissue repair mechanism. Conversely, if SARS-CoV-2 triggers dysfunctional immune response termed immunopathology, the homeostasis control mechanism becomes lost resulting in cytokine storm.^{12,13}

According to the data from World Health Organization (WHO) and John Hopkins University, the worldwide number of confirmed cases and mortality from COVID-19 were 15,090,000 and 768,600

respectively as at 16 August 2020. Clinical studies among SARS-CoV-2 infected patients have shown that cytokine storm is the principal cause of severe morbidity, poor prognosis and mortality due to COVID-19.¹⁴ Persistent marked elevation of 38 out of 48 cytokines levels measured in a longitudinal study of COVID-19 patients was observed in these patients.¹⁵ A report from cohort of 50 COVID-19 patients with severe with severe morbidity revealed that excessive production of cytokines; tumor necrosis alpha (TNF- α) and interleukin 6 (IL-6) caused by excessive activation of nuclear factor kappa B (NF κ B) transcriptional activity, coupled with impaired interferon (IFN) activity were responsible for severe morbidity due to COVID-19.¹⁶ This investigation therefore suggests combined therapeutic strategy that attenuates TNF- α and/or IL-6 coupled with IFN as possible strategies to effectively attenuate COVID-19 severe morbidity and mortality. Several therapeutic agents and strategies aimed to reduce severe morbidity and mortality due to COVID-19 through mitigating cytokine storm and hyperinflammation have been considered. Pharmacological agents such as selective cytokine blockers (TNF blockers, IL-6 antagonists, IL-1 family antagonists), corticosteroids, toll-like receptor antagonists, janus kinase inhibitors, chloroquine and hydroxychloroquine, and ulinastatin have all been identified and considered as promising agents. Therapeutic strategies through interferon therapy, convalescent plasma therapy, stem cells therapy, and blood purification therapy have also been recognized.

A therapeutic opportunity to be explored is provided by NF κ B that serves as major transcriptional factor in stimulation of cytokines genes in SARS-CoV-2 induced cytokine storm. Activation of the NF κ B signaling pathway represents a major contribution in SARS-CoV-2 induced cytokine storm and NF κ B is

Supplementary information The online version of this article ([Tables/Figures](#)) contains supplementary material, which is available to authorized users.

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well established as major transcriptional gene regulator that induces the expression of almost 400 target genes involved in inflammation in response to appropriate production stimuli.^{17,18} However, a number of factors form limitations that challenge the pre-clinical translation of NF κ B modulators to clinical management of various disease conditions, including COVID-19. The objective of this paper therefore is to explore the modulation NF κ B pathway as a strategy to mitigate COVID-19 severe morbidity and mortality, as well as discuss and offer potential solutions to various limitations that might challenge the clinical use of NF κ B modulators against COVID-19.

Cytokine storm in COVID-19 and agents that target it

Cytokine storm also known as hypercytokinemia is the excessive inflammatory reaction due to exaggerated uncontrolled response of the host's immune system.¹⁹ The term cytokine storm was first used by Ferrara et al.²⁰ to denote exaggerated cytokine production in a graft-versus-host disease where the role of interleukin 1 was considered. Cytokine storm was first implicated in an infectious disease by Barry et al.²¹ 2000 in Epstein-Barr virus-associated study and subsequently many infectious and non-infectious diseases have been linked with cytokine storm, including severe acute respiratory syndrome coronavirus (SARS-CoV)²² and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)^{23,24}

The mechanism of cytokine storm in COVID-19 results from loss of regulatory control in the host immune response subsequent to SARS-COV-2 invasion and replication. The host resident cells of the innate immunity in the lungs such as alveolar macrophages, epithelial cells and dendritic cells,²⁵ and the antigen presenting cells which are components of the adaptive immunity constituted by T and B lymphocytes,¹⁹ requires ideal activation of the inflammatory pathways through cytokine and chemokine production as key components necessary for viral elimination. This well-regulated process proceeds to play an important protective role that leads to the resolution and elimination of the virus.²⁶

Nonetheless, dysfunctional pulmonary immune response occurs in cases of SARS-COV-2 infections where the immune response becomes exaggerated

resulting in the loss of regulatory control mechanism of cytokines generation,^{27,28} with concomitant elevation in levels of pro-inflammatory cytokines resulting in significant tissue injury at both local and systemic levels. At pulmonary level, this leads to increased permeability of the alveoli resulting in unrestrained inflammatory cell infiltration and accumulation of fluids that result in physiologic alteration of alveolar gas exchange.²⁹ At systemic level, abnormally high levels of cytokines impair host response to infection that translates into sepsis culminating into septic shock and multi-organ failure.³⁰

Several studies analyzing cytokine profile from COVID-19 patients has shown that cytokine storm correlated directly with poor prognosis and severity of COVID-19.^{31,32} Studies have been consistent in establishing relationship between cytokine levels and disease progression in patients with COVID-19. COVID-19 patients in the intensive care unit (ICU) were found to have higher serum levels of macrophage inflammatory protein-1A, and TNF- α compared with COVID-19 patients from general wards indicating that cytokine storm is positively correlated with disease severity.² Serum level of IL-6 and the expression levels of IL-2R in COVID-19 patients were found to be positively correlated with the severity of the disease.²⁴ Positive regulatory loop that amplify local inflammation, including production of IL-6 and TNF- α generated by NF κ B pathway was implicated as one of the major genesis of severe form of COVID-19.¹⁶

Effective cytokine storm suppression has been suggested as modality for therapeutic intervention in severe COVID-19 infection to curtail mortality.³³ Various therapeutic agents and strategies been considered against SARS-CoV-2 induced cytokine storm. These includes selective cytokine blockers (TNF blockers, IL-6 antagonists, IL-1 family antagonists),³⁴⁻³⁷ corticosteroids,^{38,39} interferon therapy,³⁸ stem cells,⁴⁰ convalescent plasma therapy,⁴¹ blood purification therapy,³⁸ janus kinase inhibitors,⁴² toll-like receptor antagonist,⁴³ chloroquine and hydroxychloroquine (CQ/HCQ),^{44,45} ulinastatin⁴⁶ among others. A clinical trial group termed RECOVERY (Randomized Evaluation of COVid-19 thERapY) has of recent approved the use of dexamethasone, a

corticosteroid as a potent agent to improve survival in COVID-19, as it was found to reduce death by up to one third in hospitalized patients with severe respiratory complications of COVID-19.⁴⁷

NF κ B pathway and its blockers

NF κ B belongs to Rel family of proteins and is one of key transcription factor which signaling pathway activates transcription of several genes involved in inflammation and cellular immunity.⁴⁸ The NF κ B signaling pathway is initiated by the presence of wide range inflammatory stimuli as a result of infections, injury or oxidative stress. NF κ B is sequestered in the cytoplasm coupled to its inhibitory proteins collectively called Inhibitors of NF κ B (I κ B), with the prominent being Inhibitor of NF κ B alpha (I κ B- α) which inhibits the translocation to the nucleus and hence the activation of NF κ B.⁴⁹ Presence of appropriate NF κ B production signal leads to activation of cytosolic enzyme I κ B kinase (IKK) that subsequently triggers the proteolytic degradation of I κ B through enzymatic phosphorylation, thus cleaving NF κ B from its inhibitors freeing it to subsequently translocate to the nucleus, where it binds with DNA and activates transcription of cytokines, chemokines, inflammatory enzymes, and adhesion molecules among others.⁵⁰ IKK is an enzyme complex constituted by two related kinases namely I κ B kinase alpha (IKK α) and I κ B kinase beta (IKK β), and a regulatory non-enzymatic scaffold protein termed NF κ B essential modifier (NEMO) also known as IKK γ .⁵¹

Activated NF κ B complexes can be of any form of homo- and heterodimers subunits, based on the subunit dimmers released upon enzymatic activity of IKK; NF κ B signaling pathway is classified into canonical (classical) pathway and the non-canonical (alternative) pathway.^{51,52} The classical pathway is most common and IKK degradation of I κ B leads to the release p50/p65 dimers that translocate to the nucleus to induce downstream transcriptional activity.^{53,54} In this pathway signals are mostly received from the receptors such as tumor necrosis factor receptor (TNF-R), interleukin 1 receptor (IL-1R) and toll-like receptors.⁵⁵ The non-canonical pathway is less common and IKK enzymatic phosphorylation activity leads to release of p100 which subsequently

liberate RelB/p52 active heterodimers that translocate to the nucleus to activate target genes.⁵⁶ This pathway is activated by limited stimuli, mainly from lymphotoxin B and B-cell activating factor.⁵⁷

Several literatures support and expand the physiological role of NF κ B in numerous biological systems including immune responses, inflammation, antioxidant proteins in oxidative stress, cell growth and apoptosis.^{58–60} Dysregulated NF κ B activation and its signaling pathway has played a role in the pathogenesis of several disease conditions such as autoimmune diseases,⁶¹ malignancies,^{62,63} neurodegenerative diseases,^{64,65} musculoskeletal diseases,⁶⁶ and microbial diseases including infectious diseases of respiratory system caused by viruses in influenza,^{67,68} respiratory syncytial virus,⁶⁹ SARS-CoV,⁷⁰ SARS-CoV-2.^{71,72}

Cytokine storm in COVID-19 and NF κ B pathway

Cytokine storm in COVID-19 has been one of the major therapeutic targets aimed at reducing severity of morbidity and mortality due to SARS-CoV-2 infection. All patients with severe COVID-19 are required and recommended for laboratory test to screen hyperinflammation and possible cytokine storm syndrome.³⁶ Several pharmacological agents for therapeutic use against COVID-19 induced cytokine storm has been considered, with each targeted to suppress cytokine storm and attenuate severe morbidity and mortality due to the disease. Theoretical mechanism of action of such pharmacological agents and strategies has been explained. Selective cytokine blockers such as TNF blockers, IL-1 family antagonists (anakinra), and IL-6 antagonists (monoclonal antibody IL-6 receptor antagonist tocilizumab, sarilumab) directly inhibit the respective pro-inflammatory cytokine.^{36,37} Corticosteroids (methylprednisolone, dexamethasone, and hydrocortisone) possess steroid hormones-like effect of suppressing inflammation.^{38,39} Interferons (IFN- λ) confer anti-inflammatory property by acting on epithelial cells to inhibit mononuclear macrophage-mediated pro-inflammatory activity of IFN- $\alpha\beta$ signaling pathway.³⁸ Stem cells (mesenchymal stem cells) offer anti-inflammatory effect through targeting and inhibiting abnormal activation of inflammatory cells such as macrophages.⁴⁰ Convalescent

plasma or intravenous immunoglobulins serves as antibodies to salvage and facilitate infected cell immune clearance.⁴¹ Blood purification strategies aimed at removing inflammatory factors and minimize damage due to hyperinflammation.³⁸

Other pharmacological agents include Janus kinase (JAK) inhibitors (tofacitinib) which interfere with JAK signaling that activates transcription and induction of inflammatory cytokines such as IL-6 thereby interfering with its production.³⁶ Toll-like receptors (TLR1-11) antagonists interfere with TLR mediated critical role in activation of inflammatory pathways involving TLR transmembrane that activate innate immunity by recognizing pathogen associated molecular patterns.⁷³ CQ/HCQ have multifaceted anti-inflammatory mechanism including inhibition of IL-6 and TNF- α and suppression of TNF receptors, suppression of major histocompatibility complex (MCH) class II expression which obstructs T-cell activation and consequent expression of CD145 and cytokines release, and to a certain extent through obstruction of Toll-like receptors (TLRs) signaling among others to support its proposed advantage for clinical use.⁴⁵ Ulinastatin glycoprotein inhibits pro-inflammatory cytokines including interleukins (IL-1, IL-6 and IL-8), and TNF- α as one of its principle therapeutic mechanism of action to reduce ARDS and mortality.⁷⁴

It is a very imperative and wise approach to explore modulation of NF κ B pathway as potential strategy to mitigate COVID-19 severe morbidity and mortality. This is based on the fact that NF κ B pathway control the expression of numerous genes activated during inflammation such as genes for pro-inflammatory cytokines, chemokines, immune receptors, cellular ligands, adhesion molecules, metalloproteinases, acute phase proteins, and inflammatory enzymes.^{48,75-76} This makes NF κ B master regulator and most important transcription factor that plays a fundamental role in inducing wide spectrum genes involved in inflammation.^{77,78} Thus, inhibition of NF κ B pathway offers exceptional advantage of multi-levels downstream effect towards mitigating hyperinflammation and ultimately cytokine storm in COVID-19 when compared with other agents that targets single host regulatory pathway.

There exist abundant of NF κ B pathway blockers with more than 750 been identified,⁷⁹ but limitation exists in the preclinical translation of such blockers to clinical practice. A number of factors culminate to form a barrier against the effective clinical use of NF κ B pathway blockers. Firstly, lack of specificity by NF κ B blockers to spare other cellular physiological functions in the biological system orchestrated by NF κ B thereby rendering numerous adverse effects from indiscriminate NF κ B blockade.^{59,61} Secondly, the multitude complexity of NF κ B pathway signaling that serves as double-edged sword, while on one hand this complexity serves as an advantage for pharmacological agents to target different steps of the pathway as therapeutic options, on the other hand it serves as a disadvantage of possibilities to sparing NF κ B activities through shunting a particular mechanism targeted through other available pathways or dimers.⁷⁹ Thirdly, the therapeutic time window for clinical administration of NF κ B blockers that requires appropriate determination of disease progression to warrant the use in order to avoid hindering the NF κ B mediated critical role in fighting the diseases.

Despite the aforementioned limitations that challenge the effective translational use of NF κ B pathway blockers in clinical management of various diseases including COVID-19, there is still reasonable hope to consider in their use as therapeutic agents. Future research and investment into the development of tissue-specific or cell-specific NF κ B blockers such as pulmonary tissue-specific NF κ B blockade as in the case of COVID-19 might present promising strategy to minimize or avoid the unwanted side effects of non-selective NF κ B blockade. Such NF κ B blockers should target common regulatory proteins of both canonical and noncanonical NF κ B pathways as a way to curtail shunting of the therapeutic agent through the alternate NF κ B pathway. Monitoring clinical indicators of disease severity and monitoring laboratory indices of disease progression through serial tests that may herald the onset of hyperinflammation and cytokine storm in COVID-19 might provide the necessary information on dysregulation of host immunity thus providing appropriate therapeutic timing for clinical drug administration.

CONCLUSIONS

Non-pharmacological preventive strategies and supportive treatment remains the mainstay of management approach in COVID-19 pandemic as there appears to be no silver bullet for therapeutic cure at the moment. NF κ B pathway represents a multi-level regulator of numerous genes involved in COVID-19 induced cytokine storm, thus making development of cell or tissue targeted NF κ B blockers potentially promising therapeutic agents against severe morbidity and mortality in COVID-19 patients.

Future research should address the aforementioned strategies in order to circumvent the factors militating against the clinical use of NF κ B blockers against COVID-19.

INFORMATION

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