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CURRENT OPINION

Repurposing low-dose naltrexone for the prevention and treatment of immunothrombosis in COVID-19

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Coronavirus disease 2019 (COVID-19) is characterized by striking dysregulation of the immune system, with evidence of hyperinflammation, an impaired induction of interferons, and delayed adaptive immune responses. In addition to dysfunctional immune responses, thrombosis is a hallmark of severe COVID-19. Because traditional anticoagulation strategies are associated with increased bleeding, novel strategies that address both the immune and thrombotic dysfunction associated with COVID-19 would be of tremendous benefit. In this commentary, we discuss the unique properties of low dose naltrexone (LDN) which could be leveraged to reduce the immune-mediated thrombotic complications in COVID-19. Mechanistically, LDN can blunt innate immune responses and Toll-like receptor (TLR) signaling, reducing interleukin1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interferon (IFN) levels. Because of the immune-mediated thrombotic mechanisms that underlie COVID-19, we hypothesize that the immune-modulating and known pharmacologic properties of LDN could be leveraged as a novel therapeutic strategy in COVID-19.

Keywords COVID-19 • inflammation • biomarkers • thrombosis • Naltrexone

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the current pandemic has resulted in more than 240 million cases and 4.9 million deaths (as of November 2021). The clinical presentation of COVID-19 is heterogeneous, with ∼15% of patients progressing to severe disease necessitating hospitalization and organ support.[1]

SARS-CoV-2 infections begin after viral entry through the angiotensin-converting enzyme 2 (ACE2) receptor.[2] SARS-CoV-2-infected alveolar epithelial cells and alveolar immune cells produce vascular and inflammatory mediators. The innate immune system serves as the first line of defence against SARS-CoV-2 and is critical in engaging the adaptive immune system to develop durable viral immunity. With respect to SARS-CoV-2, the initial immune response is mediated by pattern-recognition receptors (PRRs) such as cytosolic RIG-I-like receptors (RLRs) and Toll-like receptor (TLR).[2] Following viral recognition, host immune responses are triggered, including the secretion of inflammatory cytokines and other defence factors. With respect to antiviral defences, type I/III interferons (IFNs) are critical mediators and work in concert with other cytokines TNF-α, interleukin-1 (IL-1β), and IL-6 to suppress SARS-CoV-2.[3]

COVID-19 and immunothrombosis

In addition to immune dysregulation, SARS-CoV-2 infections are associated with an increased incidence of thrombosis.[4] Patients with COVID-19 have a unique coagulopathy with mild thrombocytopoenia and an increase in IL-8, IL-6, TNF-α, D-dimer, and tissue factor (TF).[5] The respiratory injury associated with SARS-CoV-2 infections also affects the vasculature, resulting in endothelial damage and apoptosis.[2] This damage reduces their intrinsic antithrombotic activity, increasing the risk of thrombosis. Additionally, neutrophil extracellular trap (NET) formation is regulated by activated platelets and NETs themselves can induce macrophage release of IL-1β, enhancing both inflammation and thrombosis and accelerating organ damage in SARS-CoV-2 infections.[6] Because of the intimate link between inflammation and thrombosis in COVID-19, novel

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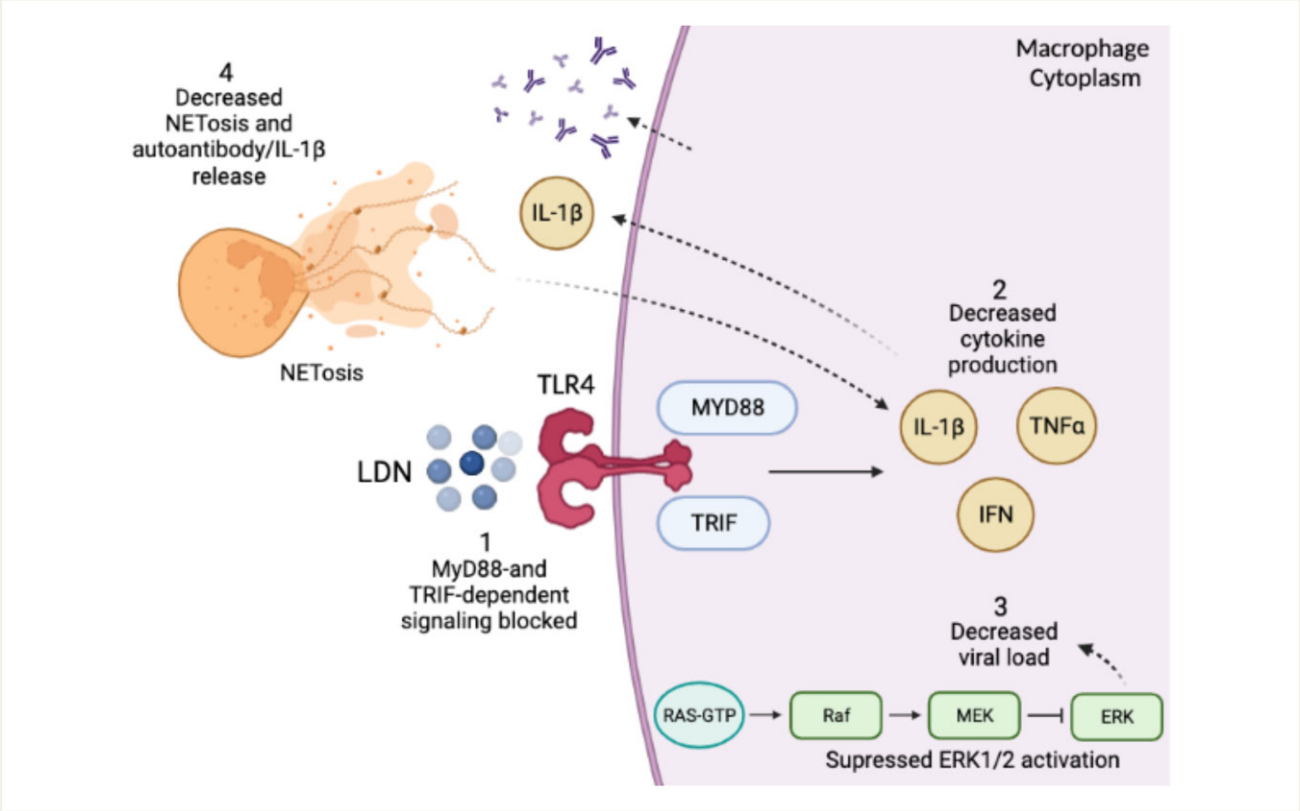

Figure 1. Potential beneficial mechanisms of low-dose naltrexone in COVID-19. (1) Low-dose naltrexone blunts MyD88-and TRIF-dependent signalling; (2) low-dose naltrexone decreases levels of IL-1, TNF-α, and IFN; (3) low-dose naltrexone suppresses ERK1/2 activation in innate immune cells and decreases SARS-CoV-2 viral load; and (4) low-dose naltrexone blocks NETosis and autoantibody production. Created with BioRender.com.

therapeutic approaches that mitigate both these dimensions in parallel have great potential to reduce the thrombotic and inflammatory burden without unwanted effects on haemostasis and bleeding.

Low-dose naltrexone in inflammatory diseases

Naltrexone (NTX), a competitive opioid receptor antagonistic, has primarily been used in the management of alcohol dependence and opioid addiction. At typical doses (50 mg), NTX inhibits activity at mu- and delta-opioid receptors, suppressing β-endorphin activity.[7] However, at low doses (between 1 and 5 mg) NTX has analgesic and anti-inflammatory properties. Because of these properties, low-dose naltrexone (LDN) has recently been used in several chronic inflammatory diseases, including inflammatory bowel disease (IBD) and multiple sclerosis, and has been shown to blunt pathologic inflammation and reduce the incidence of clinical thrombosis.[7,8] Importantly, LDN is well tolerated and its adverse effects are rare, mild, and self-limited. It is believed that LDN can also modulate other, non-opioid receptors. Perhaps the most compelling data for LDN is its use in Crohn's disease, a type of IBD that affects the GI tract.[9] In a 12-week double-blind placebo-controlled trial of LDN in 40 patients with severe Crohn's disease, there was a significant improvement in symptoms and a reduction in pathologic signs of GI inflammation in the LDN group compared with the placebo group.[10] Of the patients treated with LDN, 88% had at least a 70-point decline in their Crohn's Disease Activity Index (CDAI) score compared with 40% in the placebo group.[11] Similar to LDN's positive effects in Crohn's disease, accumulating evidence suggests LDN can reduce glial inflammation through modulation of macrophage TLR4 signaling.[8] Specifically, LDN has been shown to blunt MyD88-and TRIF-dependent signalling, leading to a decrease in IL-1, TNF-α, and IFN. In murine colitis models, LDN has been shown to have an anti-inflammatory effect in intestinal cells with a reduction in systemic IL-6, IL-12, C-reactive protein, and TNF-α, all associated with a reduction in symptoms.[12] In addition to its immune-modulating properties, NTX and LDN can modulate thrombotic responses. Previous studies have found that treatment with NTX can suppress platelet aggregation through desensitization of α2-adrenoreceptor and 5-HT2 receptor-mediated platelet aggregation.[13] Although additional randomized controlled trials are needed to evaluate the efficacy of LDN in inflammatory diseases, the immune-modulating and antithrombotic properties of LDN suggest that it could be used more broadly in inflammatory diseases, including COVID-19.

Potential immune-modulating mechanisms of LDN in COVID-19

Several risk factors for COVID-19 are associated with immune and vascular dysfunction.[14] LDN has been postulated to be of value in

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SARS-CoV-2 infections because of its ability to disrupt viral binding to the ACE2 receptor and its ability to suppress TLR-mediated induced proinflammatory cytokines.[15] LDN has the potential to inhibit the early attachment of the SARS-CoV-2 spike protein to respiratory epithelial cells. Additionally, *in vivo* studies on murine macrophages suggest that LDN can shift the balance of macrophage populations through modulation of CD64 and CD206 expression as well as through modulation of inflammatory cytokine production.[7] Studies have also found that LDN can maintain the integrity of the blood—brain barrier (BBB), which in COVID-19 could be particularly beneficial as neurologic complications and even the cytokine storm that characterizes severe COVID-19 have been linked to BBB function.[9] Additionally, LDN can suppress ERK1/2 activation in innate immune cells and suppression of ERK signalling has been associated with a decrease in viral load in COVID-19.[15] Because of the multitude of immune-modulating properties, LDN could be particularly beneficial in COVID-19.

Putative anti-thrombotic mechanisms of LDN in COVID-19

As noted above, observational studies have demonstrated an increased incidence of thrombosis in COVID-19. Multiple mechanisms underlie this propensity, including dysfunctional immune and vascular responses. LDN can positively modulate many of these thrombotic mechanisms, including its effect on innate immune responses, autoantibodies, NET formation, platelets, and fibrinogen. Endothelial damage associated with SARS-CoV-2 infections reduces endothelial cells' intrinsic antithrombotic activity.[16] Studies have suggested that opioid receptors modulate vascular function and angiogenesis, and that antagonism of opioid receptor signalling with NTX can improve endothelial cell function and induce angiogenesis.[17] The induction of NETs has been linked to pathogenic autoantibodies and IL-1β. In a cross-sectional study of patients with COVID-19, greater than 80% of patients had detectable antiphospholipid antibodies, and this was associated with an increased incidence of thrombosis.[18] Given the close relationship between innate immune cell activation and cytokines (especially IL-1β), we hypothesize that through LDN suppression of TLR-mediated inflammation, LDN can not only mitigate cytokine production but also reduce NETosis and autoantibody generation in COVID-19. Moreover, the thrombi in patients with COVID-19 have greater fibrin and complement (C5b-9) components than thrombi from non-COVID-19 patients.[19] NTX treatment has been associated with a reduction in fibrinogen, leukocyte and platelet aggregation, and coagulation markers. Specifically, Galante and colleagues found that treatment with NTX can reduce fibrinogen levels and leukocyte aggregation.[20] Both through its immune-modulating properties and its direct effects on platelet and coagulation pathways, LDN has tremendous potential to positively impact the thrombotic drivers present in COVID-19.

Summary and future directions

Despite the emergence of effective vaccines and antiviral therapies, COVID-19 continues to cause high morbidity and mortality, necessitating the development of novel therapeutic strategies. The unique immune-modulating properties of LDN coupled with its low cost and known pharmacodynamic and pharmacokinetic properties make it a particularly attractive therapeutic option for COVID-19. Through its effects on TLR signalling, pathogenic autoantibody production, and platelet/immune-mediated thrombosis, LDN could be particularly beneficial in that it counteracts several of the pathogenic drivers of COVID-19 (*Figure* 1). Furthermore, a phase 2 clinical trial (COLTREXONE) is currently underway testing the impact of anti-inflammatory agents colchicine and LDN, both alone and in combination, on disease progression in patients hospitalized with moderate COVID-19 (NCT04756128). Future mechanistic and clinical studies are needed to validate LDN targets and determine the clinical benefits of LDN (alone and in combination with existing therapies) in COVID-19.

Conflict of interest: B.P. is a consultant for Bayer, Astra Zeneca, Boehringer Ingelheim/Lilly, Merck, Sanofi/Lexicon, Vifor/Relypsa, scPharmaceuticals, SQ Innovation, G3 Pharmaceuticals, Cereno Scientific, KBP Biosciences, Sarfez Pharmaceuticals, and Phasebio, and holds stock options in Vifor/Relypsa, scPharmaceuticals, SQ Innovation, Cereno Scientific, KBP Biosciences, and Sarfez Pharmaceuticals. B.P. holds US patent 9 931 412, site specific delivery of eplerenone to the myocardium, and US patent pending 63/045 783, histone-acetylation-modulating agents for the treatment and prevention of organ damage. R.S.R. reports research grants to his institution from Amgen, Arrowhead, Novartis, and Regeneron; consulting fees from Amgen, CVS Caremark, Lilly, Novartis, and Regeneron; non-promotional honoraria from Kowa; royalties from Wolters Kluwer (UpToDate); and stock holding in MediMergent, LLC.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article.

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