MINI REVIEW ARTICLE

Melatonin and REGN-CoV2 combination as a vaccine adjuvant for Omicron variant of SARS-CoV-2

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Abstract
The omicron variant (B.529) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in late 2021, caused panic worldwide due to its contagiousness and multiple mutations in the spike protein compared to the Delta variant (B.617.2). There is currently no specific antiviral available to treat Coronavirus disease 2019 (COVID-19). However, studies on neutralizing monoclonal antibodies (mAb) developed to fight COVID-19 are growing and gaining traction. REGN-COV2 (Regeneron or imdevimab-casirivimab combination), which has been shown in recent studies to be less affected by Omicron's RBD (receptor binding domain) mutations among other mAb cocktails, plays an important role in adjuvant therapy against COVID-19. On the other hand, it is known that melatonin, which has antioxidant and immunomodulatory effects, can prevent a possible cytokine storm, and other severe symptoms that may develop in the event of viral invasion. Along with all these findings, we believe it is crucial to evaluate the use of melatonin with REGN-COV2, a cocktail of mAbs, as an adjuvant in the treatment and prevention of COVID-19, particularly in immunocompromised and elderly patients.

Abbreviations

ACE2	Angiotensin converting enzyme 2
AI	Artificial intelligence
BMAL1	Brain and muscle ARNT-like protein 1
CD147	Cluster of differentiation 147
COVID-19	Coronavirus disease 2019
COX-2	Cyclooxygenase-2
FDA	Food and drug administration
IL	Interleukins
IP10	Interferon-γ-inducible protein 10
iNOS	Inducible nitric oxide synthase
mAb	Monoclonal antibodies
MMPs	Matrix metalloproteinases
MPO	Myeloperoxidase
RAAS	Renin–angiotensin–aldosterone system
RBD	Receptor binding domain
REGN-COV2	Regeneron or imdevimab-casirivimab
ROS	Reactive oxygen species
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TGF-β	Transforming growth factor beta
TNF-α	Tumor necrosis factor-α
VEE	Venezuelan equine encephalomyelitis
WHO	World health organization

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Background

Since the World Health Organization (WHO) reported the first case of COVID-19 on March 11, 2020 [1], previously identified dominant variants of SARS-CoV-2 virus were alpha (B.7), beta (B.351), gamma (P.1) and delta (B.617.2) [2]. The Omicron SARS-CoV-2 variant, first identified in South Africa in November 2021, is said to be more contagious than previous variants [3]. Omicron is known to have a much higher number of mutations compared to another previously dominant variant, Delta [4]. Fifteen of the mutations detected in the omicron variant are in the receptor-binding domain associated with increased viral binding affinity and antibody escape [5]. Therefore, understanding the mutational hotspots of the virus plays an important role in designing effective therapeutic and preventive strategies against the new variant. Variations in spike glycoprotein sequences and their implications suggest that vaccines and coronavirus-specific binding inhibitors and adjuvant treatment options may be required for the omicron variant of SARS-CoV-2 [3–5]. Vaccine-induced immunity aims to neutralize the SARS-CoV-2 spike protein and the receptor-interacting angiotensin converting enzyme 2 (ACE2) [6]. Since the spike protein in Omicron's version contains more modifications than other variants, it could be viewed as a potential anti-vaccine immune escape option. However, immunological escape from memory T cells is unlikely to occur for non-surface proteins, after infection or vaccine-induced immunity [7, 8].

On the other hand, recent data obtained during the pandemic period suggests that complications and deaths from COVID-19 disease caused by the SARS-CoV-2 virus might be related to the high viral load that infected people are exposed to [9]. However, clinical and experimental studies continue to develop new agents against COVID-19 from a prophylactic and therapeutic point of view. Monoclonal antibodies (mAb), which can bind to and neutralize the SARS-CoV-2 virus in infected patients, are one of the new classes of treatment being studied against COVID-19 [10, 11]. REGN-COV2 (imdevimab-casirivimab combination) is one of the neutralizing mAb treatments approved by the Food and Drug Administration (FDA) for emergency use in patients with mild to moderate complications of COVID-19.[12].

One of the most important conditions that characterizes a severe SARS-CoV-2 infection is the event known as a "cytokine storm" [13]. It is an aggressive inflammatory response with the release of large amounts of pro-inflammatory cytokines accompanied by COVID-19 infection [13]. This hyperinflammatory state is often characterized by pulmonary infiltration [13, 14]. With the entry of the SARS-CoV-2 virus into alveolar epithelial cells,

the immune system stimulates CD14 + and CD16 + monocytes, alveolar macrophages and Th17 lymphocytes to release large amounts of pro-inflammatory cytokines and chemokines, including interleukins (IL) such as IL-1β, IL-6 and IL-8, tumor necrosis factor-α (TNF-α) and interferon-γ-inducible protein 10 (IP10) [13, 14]. The resulting cytokine/chemokine storm causes severe damage to the lungs, endothelial and epithelial cells. Consequently, alveolar edema may develop with a breakdown in the integrity of the blood/air barrier [14]. Additionally, fibrinogen factors such as transforming growth factor beta (TGF-β) in the presence of a cytokine storm can significantly inhibit gas exchange in the lungs due to pulmonary fibrosis [14].

Despite all these treatment strategies, due to a severe cytokine storm, COVID-19 can have fatal outcomes such as tissue damage, lung failure and multi-organ failure [13, 14]. Complementary adjunctive and immunomodulatory therapies are required to reverse immune system dysfunction and cytokine dysregulation. Melatonin is also known to have anti-inflammatory [15], antioxidant [16], immunomodulatory [17] and antiviral [18] infectious activities. It may be useful to use melatonin together with REGN-COV2 in elderly and other high-risk patients as an adjuvant to vaccines against the Omicron variant of SARS-CoV-2infection.

REGN-COV2 therapy and omicron variant

Corona viruses are known as RNA viruses that cause enzootic infections; they are particularly common in birds and mammals [19]. It is known that coronaviruses act by binding to the serine protease receptors TMPRSS2 and ACE2 on cells of the respiratory system due to the spike (S) proteins they carry [20]. Neutralizing monoclonal antibodies (mAb) used to fight the SARS-CoV-2 virus is produced by them against the receptor-binding domain of the virus spike (S) protein. Anti-RBD mAbs act by targeting the receptor-binding domain of protein S, preventing its binding to ACE2 on host cells and neutralizing its ability to fuse with the receptor [21], as shown in Fig. 1. Humanized mouse model technology or using sera from patients recovering from COVID-19 are known as preferred sources for obtaining neutralizing mAbs [22]. Concurrent studies continue to investigate the efficacy of neutralizing antibodies in hospitalized COVID-19 patients with severe symptoms [23, 24]. The REGN-COV2 antibody cocktail consists of a combination of casirivimab and indevimab, two potent neutralizing IgG1 mAbs that bind to different sites of the spike protein receptor-binding domain [25]. The main reason for using neutralizing antibodies in combination rather than alone is to avoid simultaneous inactivation of both antibodies due to mutations in SARS-CoV-2 protein S. Furthermore, the

Fig.1 REGN-COV2 (Casirivimab/imdevimab) antibody cocktail binds to the receptor binding domain (RBD) of SARS-CoV-2 virus and by neutralizing the RBD, the binding ability of the virus to ACE2 receptor is inhibited
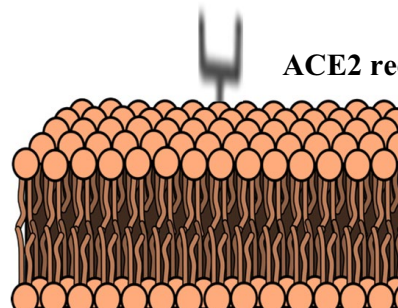

SARS-CoV-2

RBD- Antibody complex
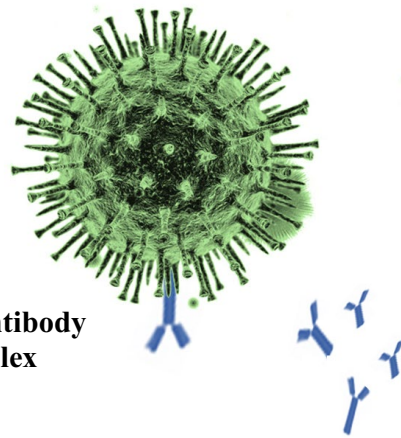
REGN-COV2 'antibody cocktail' Casirivimab/imdevimab

Antibodies block the RBD of spike protein, «neutralizing» its ability to bind ACE2

ACE2 receptor

combination of casirivimab and indevimab was tested on SARS-CoV-2-infected rhesus monkeys and golden hamsters, which served as models for SARS-CoV-2 disease, resulting in antibody-mediated cytotoxicity and cellular phagocytosis in infected cells [26]. In both models tested, there was evidence that prophylactic and therapeutic treatment with REGN-COV2 reduced viral load and lung disease severity compared to the placebo group [26].

In a recent study, it was found that the effect on REGN-COV2, also known as Regeneron mAb cocktail, is milder compared to other monoclonal antibodies [27]. In the same study, an artificial intelligence (AI) model was trained using tens of thousands of experimental data points. Based on the different three-dimensional structures of RBD-antibody complexes, we investigated how RBD mutations in the omicron variant might affect the activity of existing antibody drugs [27]. Looking at 15 known

RBD mutations (S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, N501Y, Y505H) in Omicron [4, 27] were the RBDACE2 complex and various RBD-antibody complexes also examined. The results showed that the Celltrion antibody regdanvimab could be significantly inactivated by Omicron RBD mutations E484A, Q493R and Q498R [27]. It has been shown that the E484A mutation can also greatly reduce the potency of Rockefeller University mAbs [27]. In contrast to Eli Lilly's mAb cocktail, it was clear that the antibody REGN10 (Indevimab) did not compete directly with ACE2 and it was found that the Regeneron mAbs did not overlap with each other [27]. This appears to be crucial for REGN10933 (casirivimab) as it can directly neutralize the virus. Based on these results, omicron mutations may have a much milder effect on the REGN-COV2 cocktail compared to other mAb cocktails tested [27].These results

support that REGN-COV2 can be used as a first option in monoclonal antibody-assisted therapies.

Melatonin and importance of circadian rhythm in COVID-19

Chronotherapy could play an important role in the treatment of COVID-19 patients, a new concept in medicine that is gaining popularity today [28]. According to this concept, patients receive medication according to their circadian rhythm. In this way, as well as being able to achieve the same effectiveness at a lower dose, the medication administered can also reduce the side effects of other medications used at the same time. All these factors could optimize the therapeutic effect of the chronotherapy method. The SARS-CoV-2 virus uses endogenous cholesterol, for invasion of lung epithelial cells [29]. It is known that cholesterol production in the body peaks at night [30]. A recent study reported that statin drugs that decrease cholesterol biosynthesis by inhibiting HMGCoA reductase minimize the severe side effects of COVID-19 [31]. As a result of this study, it was observed that nighttime administration of the same dose of statins significantly reduced cholesterol levels in COVID-19 patients compared to the morning test group. Combined with all these findings, the same method could be applied to other drug groups that can be used in the treatment of SARS-CoV-2 infection and maximize the therapeutic effect.

The SARS-CoV-2 virus disrupts the function of circadian clock genes known as brain and muscle ARNT-like protein 1 (BMAL1) [32]. The decrease in the level of the BMAL1 gene, which is a regulator of the circadian rhythm, triggers the events leading to the cytokine storm by NFκB and causes the activation of pro-inflammatory cytokines [33]. Zhuang et al. demonstrated the relationship and role of circadian rhythms in altering the susceptibility of lung epithelial cells to SARS-CoV-2 infection [34]. According to this study, deletion of the essential circadian transcription activator BMAL1 resulted in lower expression of the primary viral receptor ACE2 and viral entry into lung epithelial cells.

Decreased BMAL1 levels lead to disruption of the renin–angiotensin–aldosterone system (RAAS) pathway and tissue damage [35]. BMAL1 deficiency also triggers increased production of pro-inflammatory cytokines such as TNFα [36]. Since elevated cytokine levels are important biomarkers that indicate the severity of coronavirus infection, it is important to develop a treatment strategy that takes into account BMAL1 and NFκB signaling in the management of COVID-19 disease [33, 36]. For the management of the NFκB signaling pathway, melatonin acts as a key molecule to antagonize the reduction in the levels of the Bmal1 gene, which induces a series of events leading to the cytokine storm [33]. The protective and anti-inflammatory effects of

melatonin make it a notable therapeutic option to enhance host defense response against viral invasive conditions in COVID-19.

Melatonin is a hormone produced by the pineal gland at night and plays an important role in the circadian rhythm [37]. It is known that melatonin reduces the hyperinflammatory response by inhibiting not only NFκB activity but also the interferon gamma response [38]. The fact that melatonin is readily available, inexpensive, and has a high safety profile makes it a suitable drug of choice for use against infections.
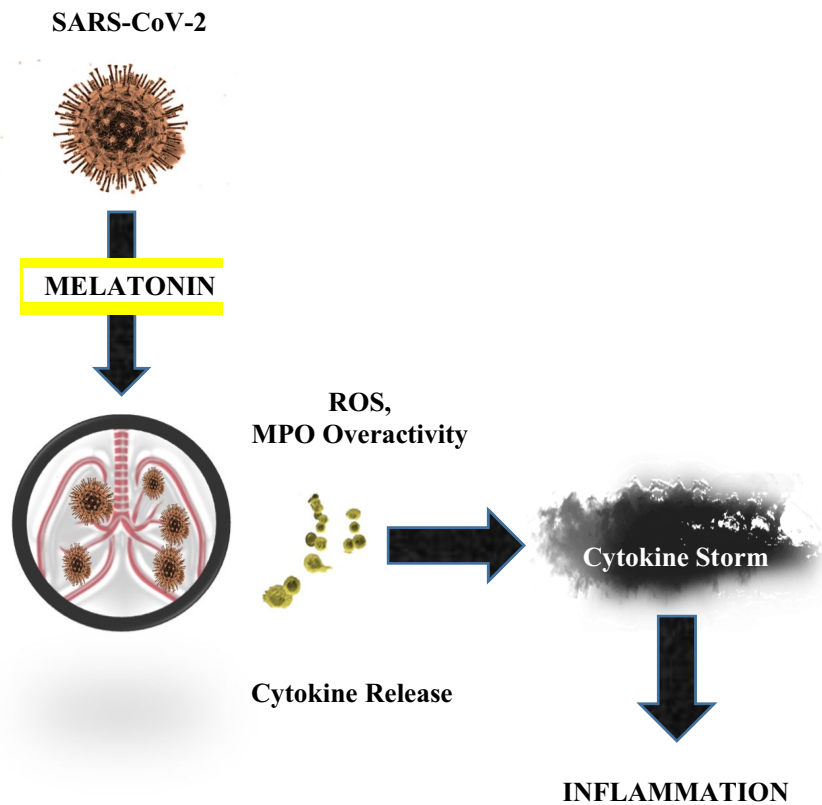
In addition to its anti-inflammatory effect, melatonin is known for its antidepressant, anxiolytic, immunomodulatory and antioxidant effects [39]. Another important role of melatonin is that it has a potent hydroxyl radical scavenging effect, particularly by increasing the activity of antioxidant enzymes such as glutathione in the antioxidant system [40]. In addition, various immune functions are modulated by melatonin. Exogenous administration of melatonin has been shown to increase antibody production [41]. Melatonin has stimulatory and suppressive effects on the immune system [42]. Specifically, it stimulates the immune system by increasing T cell activation and humoral response. In addition, it shows an immunosuppressive effect by reducing the activities of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) enzymes, which play an important role in inflammation [43].

The effects of melatonin in viral infections

Melatonin has indirect antiviral effects due to its anti-inflammatory, antioxidant, and immune-boosting properties [15]. Recent studies have shown that melatonin regulates levels of cytokines that play important roles in the immune system, such as interleukin 2 and IFNγ, in mice during Venezuelan equine encephalomyelitis (VEE) virus infection [44]. As a result of the studies, it was found that melatonin reduces viral potency and also reduces acute lung damage in respiratory syncytial virus models by inhibiting oxidative damage. A recent study showed that interleukin 2 (IL2) and IFNγ are specific biomarkers of the cellular response to SARS-CoV-2 [45]. Related to these findings, melatonin may reduce the effectiveness of the virus by showing similar activity in the SARS-CoV-2 virus.

SARS-CoV-2 has been reported to use the Cluster of differentiation 147 (CD147) S protein pathway to enter host cells [46]. CD147 is a glycoprotein that causes a cytokine storm and tissue damage in the lungs upon viral invasion. CD147 plays an important role in inflammation mediated by pro-inflammatory cytokines. In patients with COVID-19 infection, these cytokines are released uncontrollably, causing a cytokine storm [47]. Cytokine storm syndrome is caused by a variety of inflammatory conditions, including

Fig.2 Melatonin prevents the cytokine storm and inflammation by inhibiting ROS production, overactivity of myeloperoxidase and excess cytokine release

Antioxidant and anti-inflammatory effects of melatonin in cytokine storm

As the SARS-CoV-2 virus develops cytokine storm and acute respiratory distress syndrome by binding to ACE2 receptors, the oxidative reactions that occur in cytokine storm syndrome cause reactive oxygen species (ROS)-mediated lung damage [49]. The immune system can become more susceptible to SARS-CoV-2 infection as it becomes compromised with age and major comorbidities such as diabetes, cancer, heart problems [50]. Factors implicated in the onset of COVID-19 infection include a particularly compromised immune response, pathogenicity of new viral variants, and uncontrolled production of ROS associated with a cytokine storm [49]. By using melatonin, reactive

severe systemic inflammation, hemodynamic instability, and multiple organ failure. With an age-related weakened immune system and declining melatonin levels, middle-aged and elderly patients with chronic diseases are much more susceptible to respiratory arrest from SARS-CoV-2 infection. In some clinical studies, melatonin has been shown to stimulate a large decrease in the levels of cytokines, IL-6, IFN-γ and C-reactive protein, which have important effects on the CD147-mediated inflammatory pathway [48].

oxygen species and the production of free metal ions can be significantly reduced. Therefore, harmful conditions such as DNA damage, protein oxidation and lipid peroxidation can also be prevented. Reactive oxygen species cause an increase in the expression of matrix metalloproteinases (MMPs) [51]. ROS removed by melatonin supplementation may reduce the deleterious effects of MMP overexpression. In addition, melatonin can protect against inflammation in the lungs resulting from COVID-19 by suppressing oxidative stress and cell apoptosis [52]. In previous studies it was reported that the antioxidant capacity of melatonin is higher compared to other known ROS scavengers such as lycopene, methionine, taurine and uric acid [49, 53]. In addition, the severity of the effects caused by the pro-inflammatory cytokines released in the cytokine storm following SARS-CoV-2 infection is related to the degree of inflammation. Myeloperoxidase (MPO) activity and ROS production have important effects that enhance the inflammatory immune response [54]. Inhibition of MPO and removal of unwanted ROS are important therapeutic targets against SARS-CoV-2 infection, as shown in Fig. 2.

Melatonin acts by inhibiting allosteric binding and chlorination activity at the entrance of the myeloperoxidase heme pocket [55]. The cytokine storm that develops due to COVID-19 causes the MPO enzyme to work overactive. MPO hyperactivity is one of the main sources of HOCl, one of the

important reactive oxygen species [56]. Therefore, melatonin plays a beneficial role in disease treatment by scavenging released HOCl or reducing ROS-induced metal release [49, 57]. In addition, melatonin, which plays an important role in ROS detoxification, can be considered a powerful adjuvant to combat COVID-19 infection.

In addition, when melatonin is used with other drugs in the treatment of COVID-19, it enhances the effects of other drugs and reduces the potential for their side effects [58]. Melatonin has been shown to be safe for short-term use, even at high doses [59]. Therefore, the use of melatonin can be suggested as a safe treatment modality along with other drugs against SARS-CoV-2 infection. the treatment of COVID-19 as an adjuvant therapy.

Conclusion

While vaccines are the best strategy to prevent COVID-19, combination therapy of melatonin and REGN-CoV2 before or after exposure to the Omicron variant may offer significant benefits for elderly and chronically ill patients. Nursing ward admissions have increased due to the greater contagion of the Omicron variant. Therefore, infections caused by Omicron should not be underestimated and the importance of vaccination especially in high-risk patients should be emphasized. Additionally, when we consider the cost and time involved in developing a vaccine that targets new variants, identifying and expanding treatment options is extremely important. In conclusion, combined therapy of melatonin and REGN-CoV2 is an attractive approach with potential benefits in both prophylactic and therapeutic strategies as an adjuvant to vaccines for immune boosting and circadian rhythm regulation against the Omicron variant.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval Not applicable.

Consent for publication Not applicable.

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