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Review Article

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The Concomitant Use of Melatonin and Bebtelovimab as a Treatment Strategy for Omicron and Future Variants of Concern

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ABSTRACT

The number of hospitalizations and fatalities brought on by COVID-19 has considerably grown since the World Health Organization proclaimed the disease as a global pandemic. New combination therapy is required to lessen the risk of COVID-19 progression during this time when the danger of transmission rises as new Omicron sub-variants arise. In this situation, it is critical to boost the immune system to combat highly inflammatory conditions like the cytokine storm brought on by COVID-19. Furthermore, if administered early in COVID-19 illness, monoclonal antibodies (mAbs) that neutralize SARS-CoV-2 can minimize the chance of hospitalization. LY-CoV1404 (bebtelovimab) is one of these mAbs that has recently gained prominence due to its ability to effectively neutralize the SARS-CoV-2 virus and protect binding to spike proteins of several variants including B.1.1.529 (Omicron) and its subvariants (BA.1, BA.1.1, and BA.2) with various essential receptor binding domain (RBD) mutations. This brief review emphasizes the advantages of combining melatonin with bebtelovimab, which has been demonstrated to be the most effective SARS-CoV-2 neutralizing monoclonal antibody against the Omicron variant in the management of COVID-19. This study suggests that the combination therapy for Omicron sub-variants is beneficial and could be regarded as adjuvant therapy for COVID-19 disease.

Key words: *Melatonin, Cytokine storm, Monoclonal antibodies, Bebtelovimab, SARS-CoV-2*

INTRODUCTION

The World Health Organization (WHO) declared coronavirus disease (COVID -19) a pandemic in early March 2020 [1]. Since then, thousands of people have suffered and died from COVID-19 [1, 2]. SARS-CoV-2 has developed more as the pandemic has spread, as expected. Numerous variants are considered to have been produced by selective pressures and viral adaptability during protracted, inadequately treated infections; some of these mutations dramatically reduce the efficacy of COVID-19 therapeutic countermeasures [3]. Variants of concern (VOC) form a highly observed subset of numerous SARS-CoV-2 variants. This is because of their enhanced infectious potential, their high capacity to evade vaccination-induced immunity, and their tendency to reduce the efficacy of antibody-based therapies [3]. In addition, the Omicron variant was classified as a variant of concern by the World Health Organization in November 2021 [4]. This variant is in charge of increased infectiousness and lower efficacy of current therapies [4]. Omicron (B.1.1.529) is a novel SARS-CoV-2 variant with more mutations than existing variants, leading to a sharp rise in cases following its initial identification [5]. Therefore, it is urgently necessary to develop novel COVID-19 treatment methods that will both lessen the virus's efficacy and eradicate severe inflammatory conditions like cytokine storms caused by the virus.

The viral structural protein spike (S) binds to ACE2 receptors and allows the single-stranded RNA-enveloped virus SARS-CoV-2 to escape the cell [6]. The S protein serves as a bridge for entrance into the cell by the host transmembrane serine protease type 2 (TMPRSS2) [6]. Once within the cell, the replicase-transcriptase complex

is encoded by viral polyproteins. SARS-CoV-2 triggers an inflammatory response, cytokine storm, and acute respiratory distress syndrome when it binds to the ACE2 receptors and the TMPRSS2 for S-protein priming in airway epithelial cells [7]. Numerous inflammatory diseases, such as severe systemic inflammation, hemodynamic instability, and multiple organ failure, can lead to cytokine storm syndrome [7]. In addition, oxidative reactions harm the lungs, particularly the alveoli, by producing reactive oxygen species (ROS) [8]. A primary way of strengthening the virus' resistance is connected to the biological rhythm, which is used as a therapeutic strategy. The most fundamental and significant circadian rhythm is the cycle of sleep and wakefulness [9]. The hormone melatonin, which the brain primarily releases at night, supports the maintenance and rhythm regulation of the body's biological clock [10]. The immune system can combat viral infections when the lungs, heart, kidney, and brain have synchronized circadian rhythms [9].

On the other hand, a novel monoclonal antibody called bebtelovimab is intended for individuals with mild to severe COVID-19 disease severity [11]. Bebtelovimab, which is among the recombinant neutralizing monoclonal antibodies, similarly binds to the S protein of the virus. However, it is more effective against the more recent SARS-CoV-2 variants [11]. The National Institutes of Health (NIH) recommends giving high-risk patients a single 175 mg IV injection of bebtelovimab over 30 seconds [12]. Currently, in vitro tests have proven that bebtelovimab is effective against B.1.1.529 subvariants. The possible mechanistic pathway for bebtelovimab and melatonin is shown in **Figure 1**.

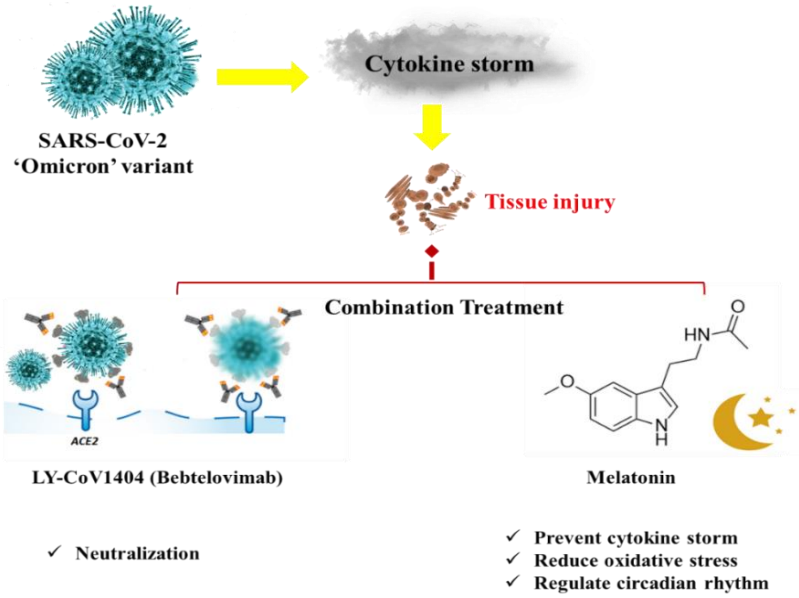

Figure 1. The mechanistic pathway for bebtelovimab and melatonin combination therapy

RESULTS AND DISCUSSION

Effect of mAb therapy and bebtelovimab against Omicron variant

It has been shown that several particular mutations within the S protein decrease the binding and efficiency of antibody treatments [13]. Understanding effective antibody treatments for neutralizing antigenic determinants in response to viral variants is critical. Antibody treatments have been shown in clinical trials to be successful in lowering the intensity of disease symptoms and avoiding mortality [14]. It is unclear whether immunizations will dramatically change the virus's mutation profile. Finding alternative medications and adjuvant therapies to treat viral mutations is vital as vaccination gains traction all over the world. According to a hypothesis, certain mutations may have developed in immunocompromised people, giving the virus more time to continue replicating and accumulate mutations, leading to the emergence of these unique VOCs [15]. For these immunocompromised patients, a potent neutralizing monoclonal antibody would be a promising treatment option since it quickly neutralizes the virus, protecting the patient and reducing the chance of viral mutation and evolution.

Viral surface spike glycoproteins target monoclonal antibodies, which stop the virus from entering host cells [16]. Contact between the host ACE2 receptor and the viral spike protein causes the virus to start penetrating host cell membranes [16]. Neutralizing mAbs potentially prevents this interaction [17]. The majority of mAbs discovered so far are directed against the receptor binding domain of viral spike protein [17]. This domain mediates the spike-

ACE2 receptor. However, neutralizing antibodies that target other spike protein areas should also exist, according to our present understanding of MERS-CoV and SARS-CoV [18]. Many studies have shown that antibody-based COVID-19 medicines are clinically safe and effective and can potentially reduce the pressure on economies and healthcare infrastructures during the pandemic [19, 20]. Immunocompromised patients, particularly vulnerable owing to comorbidities, and those over 65 are key target populations for such monoclonal antibody therapy [21]. Among the treatments targeting SARS-CoV-2, many studies are being conducted on monoclonal antibodies targeting the spike protein of the virus [22, 23]. Numerous SARS-CoV-2 mutations have variable degrees of impact on the in vitro binding of clinically evaluated or approved emergency use antibodies [24]. The most significant effects on the functioning of antibodies and vaccinations were caused by mutations at amino acid residues 417, 439, 452, 484, and 501, respectively [11, 25]. Therefore, newly developed monoclonal antibodies should maintain their strong neutralizing activity even in the presence of multiple mutations.

In a study, the neutralizing effects of various monoclonal antibodies were compared against the B.1.1.529 variant and the Wuhan strain [26]. Most of the neutralizing mAbs showed a total loss of neutralizing activity, which is consistent with the findings reported by Planas *et al*. [27]. When compared to the Wuhan strain, Sotrovimab and Evusheld (cilgavimab + tixagevimab) both showed a reduction in neutralizing activity against Omicron of less than two-fold and 100-fold, respectively [11, 26]. These findings highlight the need to develop neutralizing mAbs targeting RBD epitopes with low mutation rates. Now, bebtelovimab is the only neutralizing mAb that has been demonstrated to have substantial neutralizing efficacy against the Omicron strain [11, 28]. Furthermore, different mAbs authorized for clinical usage in SARS-CoV-2-infected patients underwent neutralization testing in a research conducted in December 2021 to assess their effectiveness against Omicron [29]. The neutralizing activities of all the tested mAbs were lost entirely. On the other hand, none of the tested monoclonal antibody cocktails affected Omicron [29].

The completely human IgG1 monoclonal SARS-CoV-2 antibody, bebtelovimab, was reported to neutralize every known VOC of SARS-CoV-2, including Omicron and its subvariants (BA.2, BA.2.12.1, BA.4, and BA.5) [30]. On February 11, 2022, the US FDA also granted Bebtelovimab an emergency use authorization [11, 30]. The epitope that bebtelovimab binds to is mainly different from the mutations extensively circulating throughout the recently discovered variants, particularly those mutations that decrease the efficacy of vaccinations [30, 31]. Notably, the interaction between the S protein and bebtelovimab is mediated by amino acids infrequently altered in the worldwide GISAID EpiCoV database, suggesting that bebtelovimab may provide a long-term remedy for lowering COVID-19-related sickness and mortality [11]. A recent study revealed that bebtelovimab successfully neutralized the virus [32], although bamlanivimab (LY-CoV555), another promising neutralizing antibody, showed less potent action than bebtelovimab [11]. Concerns have been raised about the effectiveness of some commercially tested therapeutic monoclonal antibodies due to the fast dissemination of the Omicron variant, which includes 35 mutations in the spike protein of the receptor binding domain [33].

The capability of different monoclonal antibodies to neutralize the Omicron variant was evaluated in pseudotyped neutralization studies. Only bebtelovimab maintained its complete effectiveness against the Omicron variant in these tests [11]. Furthermore, the neutralization of the Omicron subvariant known as BA.2 was investigated, and it was discovered that bebtelovimab still had activity against this variant [11]. The statistics show that bebtelovimab is still effective against VOCs, even widespread or spreading quickly. Given that numerous other effective neutralizing antibodies have been proven to lose their capacity to neutralize a range of mutations [13], it appears that bebtelovimab may be particularly well-suited to fight the existing variants. Additionally, the mutations in B.1.1.529, notably G446S, N440K, Q498R, and N501Y, located within the binding epitope [34], did not affect the neutralizing activity of bebtelovimab. Notably, strong efficacy against all tested variants indicates that bebtelovimab binds exclusively to an epitope with minimal alterations and is not susceptible to mutations that have developed. These findings further suggest that bebtelovimab, given the limited mutational activity seen to date in its binding epitope, is not only expected to continue its effective neutralizing activity against current variations but is also less likely to be affected by future mutations. In addition to vaccines and existing COVID-19 therapeutics, this mAb may offer a viable therapeutic alternative against the Omicron variant and emerging variants due to its distinctive binding epitope.

Effects of melatonin on the immune system in COVID-19

To optimize health advantages and reduce adverse consequences, chronotherapy, also known as circadian medicine or chronomedicine, aims to treat patients during the best time of day [35]. The goal of chronotherapy is to maximize medical interventions while considering the organism's circadian cycles [35, 36]. Even minor

biological clock dysfunction can have a significant impact on sleep/wake physiology by increasing diurnal somnolence, increasing sleep onset latency, delaying or advancing the phase of sleep onset, waking up frequently at night, decreasing sleep efficiency, delaying and shortening rapid eye movement sleep, or increasing periodic leg movements [36]. Through good sleep hygiene, scheduled light exposure, and the use of chronobiotic drugs like melatonin that influence the output phase of circadian rhythms, so managing the clock, chronotherapy seeks to restore the appropriate circadian pattern of the sleep-wake cycle [37]. Cycles of sleep and wakefulness, hormone release, and metabolism are only a few examples of the 24-hour rhythms of physiology and behavior produced by circadian clocks, which are biological timing processes [37]. Targeting circadian rhythms for illness prevention and therapy is becoming viable as molecular and cellular processes behind circadian physiology and pathology are more understood.

A previous study revealed the connection between circadian rhythms and how they affect lung epithelial cells' susceptibility to SARS-CoV-2 infection [38]. This study showed that deletion of Brain and Muscle ARNT-like Protein-1 (BMAL1), a critical circadian transcriptional activator, reduced expression of the major viral receptor ACE2 and virus entry into lung epithelial cells. As demonstrated in COVID-19, decreased expression of the BMAL1 gene, which controls circadian rhythms, sets off a chain of events that causes cytokine storms via the NF-κB pathway [39]. SARS-CoV-2 has been demonstrated to interact directly with Cluster of Differentiation 147 (CD147), a type I transmembrane protein implicated in viral infection, in addition to the interaction between the S protein and ACE2 [40]. Due to its well-known anti-inflammatory, immunomodulatory, and antioxidant effects, melatonin is an excellent treatment alternative to prevent severe COVID-19 symptoms [41]. Melatonin does not have direct antiviral properties. However, it does have indirect antiviral properties through antioxidant, immunoprotective, and anti-inflammatory activities [40, 41]. It has also been demonstrated that melatonin regulates serum IL-2 and IFN-α levels, which are significant actors in the CD147-mediated inflammatory pathway, reducing acute lung damage, virus-mediated stroke and death, and viral activity [40].

Melatonin is a potent stimulant of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase and provides significant protection against oxidative damage to cells [42]. The antioxidant enzymes glutathione peroxidase and superoxide dismutase are powerfully stimulated by melatonin, which offers essential protection against oxidative cell damage. Spleen cells have also been found to contain melatonin receptors (MT2) [43]. In rodents, including mice, voles, and hamsters, external administration of melatonin has been shown to stimulate the proliferation of spleen cells, with MT2 receptors playing a significant part in this stimulatory impact of melatonin [44]. Treatment with melatonin also promotes T cell proliferation [45]. When melatonin is administered to aged mice, thymus gland function and T cell-mediated immune functions reach the same level as in young mice. Melatonin decreases T cell apoptosis and increases the expression of T cell-mediated cytokines [45].

COVID-19 causes cytokine storm syndrome and acute respiratory distress syndrome (ARDS) due to the uncontrollable production of inflammatory mediators [46]. Melatonin is thought to lessen this cytokine storm by boosting the activity of natural killer cells while lowering reactive oxygen species, the interferon-gamma response, and T-helper cells [47]. Melatonin, like corticosteroids, lowers NF-κB activity to reduce the hyperinflammatory response to some respiratory infections [40]. It also enhances the production of interleukins at higher dosages [48]. These interleukins enhance the inflammatory response induced by lung infection caused by viral infections. According to a previous study, melatonin inhibited the generation of malondialdehyde and nitric oxide in mice infected with respiratory syncytial virus (RSV), which explains why there was a reduction in acute oxidative damage in the lungs [49].

Effects of melatonin as an antioxidant and anti-inflammatory agent in COVID-19

Since the SARS-CoV-2 virus causes cytokine storm and acute respiratory distress syndrome by binding to ACE2 receptors, oxidative responses in the syndrome induce reactive oxygen species (ROS)-mediated lung damage [50]. Viral infections produce reactive oxygen species. Old age and significant co-morbidities such as diabetes, cancer, and heart issues may make the immune system more vulnerable to SARS-CoV-2 infection [47]. Affected immune responses, the pathogenicity of novel viral variants, and unstable and uncontrolled generation of ROS related to cytokine storms are all factors in the development of COVID-19 infection [50]. Melatonin can considerably decrease reactive oxygen species and free metal ion generation. As a result, detrimental consequences such as DNA damage, protein oxidation, and lipid peroxidation can be avoided [50].

Matrix metalloproteinase (MMP) expression is increased due to reactive oxygen species [1]. The negative consequences of excessive MMP production can be significantly diminished by melatonin supplementation with ROS scavenging action [1, 40]. Melatonin could help to alleviate the pulmonary inflammation brought on by

COVID-19 by reducing oxidative stress and cell death. According to the studies, melatonin has a higher level of antioxidant activity than other well-known ROS scavengers [1]. Additionally, the severity of the effects induced by pro-inflammatory cytokines produced in the cytokine storm brought on by SARS-CoV-2 infection is associated with the intensity of the inflammatory immune response [50]. A heme protein called myeloperoxidase (MPO), which is found in neutrophils, uses chloride (Cl-) in the presence of H_2O_2 to produce hypochlorous acid (HOCl) [42]. HOCl is a powerful oxidant that can act as a potent antibacterial in typical conditions [1]. However, when ROS generation may increase excessively in many inflammatory conditions, HOCl can mediate tissue damage [42]. ROS generation and MPO activity have significant impacts that boost the inflammatory immune response. MPO inhibition and undesired ROS removal are crucial therapeutic targets for treating SARS-CoV-2 infection [1]. Melatonin prevents allosteric interaction and chlorination at the MPO enzyme's heme pocket entry [1, 40].
Melatonin can also be considered a potent augmenting agent to combat COVID-19 infection because of its crucial involvement in ROS detoxification [40]. The cytokine storm caused by COVID-19 promotes the overactivity of the MPO enzyme. One of the primary causes of HOCl, a significant reactive oxygen species, is excessive MPO activity [42]. Melatonin, therefore, has a therapeutic effect on COVID-19 via reducing HOCl production or metal release induced by ROS. Furthermore, it has been observed that when melatonin is used with other medications in the treatment of COVID-19, it boosts the effectiveness of these treatments while decreasing the possibility of adverse effects [1, 48]. Melatonin also dramatically reduced circulating cytokine levels in other disorders with high levels of inflammation besides COVID-19 [47, 48]. In light of all of this evidence, it has been demonstrated that melatonin is safe for short-term usage, even at high dosages [48]. As a result, melatonin supplements, which can correct poor circadian rhythms caused by aging and environmental factors, will effectively treat COVID-19 as an adjuvant to vaccines. Given this knowledge, it is possible that melatonin, in combination with bebtelovimab, might be employed as a safe treatment approach for SARS-CoV-2 infection.

CONCLUSION

The greatest method for preventing COVID-19 is vaccination. However, for the elderly and patients with chronic illnesses, melatonin and bebtelovimab combination treatment can have a considerable positive impact before or after exposure to the Omicron variant. Despite having a milder appearance, the Omicron variant's enhanced contagiousness has increased overall emergency room visits, hospital stays, and critical care unit admissions. As a result, Omicron infections should not be taken lightly, and the value of immunization should be stressed, particularly in high-risk individuals. Additionally, it is crucial to discover and increase treatment alternatives while considering the expense and time needed to produce a vaccination that targets new variations. Bebtelovimab could be employed in clinical treatment, especially in immunocompromised patients, after being compared to the dominant variations in independent clinical research and other therapeutic alternatives. In conclusion, melatonin and bebtelovimab combination therapy could be an attractive approach with potential benefits as a vaccine adjuvant to improve the immune system and to regulate the circadian rhythm against Omicron and possible future variants of concern.

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