Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2023, Volume 3, Page No: 28-35

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Therapeutic Implications of Melatonin and Bebtelovimab Combination for Omicron and Future Variants of Concern

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Received: 04 March 2023; **Revised:** 28 May 2023; **Accepted:** 29 May 2023

ABSTRACT

Since the World Health Organisation declared COVID-19 a global pandemic, the number of hospitalisations and deaths caused by the virus has significantly increased. As additional Omicron sub-variants emerge, the likelihood of transmission increases, necessitating the need for new combination therapy to reduce the risk of coronavirus development. In this case, strengthening the immune system is essential to fight against extremely inflammatory diseases such as the cytokine storm caused by the coronavirus. In addition, monoclonal antibodies (mAbs) that neutralise SARS-CoV-2 can reduce the risk of hospitalization if administered early in COVID-19 illness. One such mAb that recently gained consideration is LY-CoV1404 (bebtelovimab), which neutralises the SARS-CoV-2 virus and protects binding to the spike proteins of multiple variants, including B.1.1.529 (Omicron) and its subvariants (BA.1, BA.1.1, and BA.2) with different essential receptor binding domain (RBD) mutations. The benefits of melatonin in conjunction with bebtelovimab, the most potent SARS-CoV-2 neutralising monoclonal antibody against the Omicron form in the treatment of COVID-19, are highlighted in this brief overview. According to this study, the combination therapy is beneficial for the Omicron sub-variants and may be used as an adjuvant therapy for the coronavirus.

Keywords: Melatonin, Cytokine storm, Monoclonal antibodies, Bebtelovimab, SARS-CoV-2

How to Cite This Article: Erdag D. Therapeutic Implications of Melatonin and Bebtelovimab Combination for Omicron and Future Variants of Concern. Ann Pharm Pract Pharmacother. 2023;3:28-35. https://doi.org/10.51847/jwjMRXHjuT

Introduction

Early in March 2020, the World Health Organisation (WHO) proclaimed COVID-19 to be a pandemic [1]. Since then, COVID-19 has caused suffering and death for thousands of people [1, 2]. As anticipated, SARS-CoV-2 has evolved more as the pandemic has expanded. Selective pressures and viral adaptability during prolonged, poorly treated infections are thought to have produced a large number of variations, some of which significantly impair the effectiveness of COVID-19 treatment countermeasures [3]. Of the several SARS-CoV-2 variants, variations of concern (VOC) are a highly observed subset. Their propensity to lessen the effectiveness of antibody-based treatments, their increased infectious potential, and their high ability to avoid vaccination-induced immunity are the reasons for this [3]. Furthermore, in November 2021, the World Health Organisation designated the Omicron form as a variation of concern [4]. This mutation is responsible for the current medicines' decreased efficacy and increased infectiousness [4]. A significant increase in cases occurred after the initial identification of Omicron (B.1.1.529), a new SARS-CoV-2 variant that had more mutations than other variations [5]. Thus, it is imperative to create new COVID-19 treatment strategies that will reduce the virus's effectiveness and eliminate serious inflammatory diseases like cytokine storms brought on by the virus.

The single-stranded RNA-enveloped virus SARS-CoV-2 can leave the cell through the binding of the viral structural protein spike (S) to ACE2 receptors [6]. The host transmembrane serine protease type 2 (TMPRSS2) uses the S protein as a bridge to enter the cell [6]. Viral polyproteins encode the replicase-transcriptase complex once it is inside the cell. SARS-CoV-2 induces 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, haemodynamic instability, and multiple organ failure, can cause cytokine storm syndrome [7]. Moreover, oxidative activities generate reactive oxygen species (ROS), which harm the lungs, particularly the alveoli [8]. The biological rhythm is associated with a basic strategy for strengthening the virus's resistance as a therapeutic approach. The most fundamental and significant circadian rhythm is the cycle of waking and sleeping [9]. The body's biological clock is maintained and rhythmically regulated by the hormone melatonin, which is mostly released by the brain during the night [10]. When the circadian rhythms of the brain, kidney, heart, and lungs are in sync, the immune system can fight off viral infections [9].

Conversely, bebtelovimab, a new monoclonal antibody, is designed for people with mild to severe COVID-19 disease [11]. The recombinant neutralising monoclonal antibody bebtelovimab binds to the virus's S protein similarly. But it works better against the newer strains of SARS-CoV-2 [11]. For high-risk patients, the National Institutes of Health (NIH) advises administering a single intravenous infusion of 175 mg of bebtelovimab over 30 seconds [12]. Bebtelovimab is now effective against B.1.1.529 subvariants, according to in vitro experiments. Figure 1 depicts the potential mechanistic pathway for melatonin and bebtelovimab.

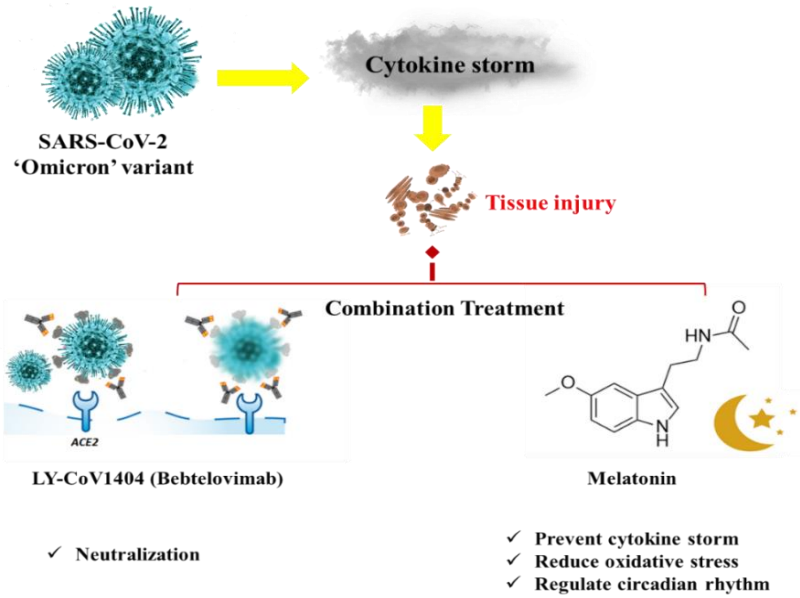

Figure 1. The mechanism underlying the combination therapy of bebtelovimab and melatonin

The present study aims to investigate the use of melatonin and bebtelovimab as a therapeutic approach for Omicron and its future variants of concern.

Results and Discussion

Effect of mAb therapy and bebtelovimab against the Omicron variant

It has been demonstrated that several specific mutations in the S protein reduce the effectiveness and affinity of antibody therapies [13]. It is essential to comprehend how to neutralise antigenic determinants in response to viral variations using efficient antibody therapies. Clinical trials have demonstrated the effectiveness of antibody therapies in reducing the severity of illness symptoms and preventing death [14]. Whether vaccinations will significantly alter the virus's mutation profile is unknown. As vaccination becomes more popular worldwide, it is critical to find alternative drugs and adjuvant therapy to cure viral infections. It is hypothesised that specific mutations may have arisen in immunocompromised individuals, allowing the virus more time to multiply and accumulate mutations, ultimately resulting in the formation of these distinct volatile organic compounds [15]. A strong neutralising monoclonal antibody would be a viable treatment option for these immunocompromised people since it neutralises the virus early, protecting the patient and lowering the likelihood of viral evolution and mutation.

Monoclonal antibodies are the target of viral surface spike glycoproteins, which prevent the virus from infecting host cells [16]. The virus begins to penetrate host cell membranes when the viral spike protein and the host ACE2 receptor come into contact [16]. This interaction may be avoided by neutralising mAbs [17]. Most of the monoclonal antibodies found to date target the viral spike protein's receptor binding domain [17]. The spike-ACE2 receptor is mediated by this domain. However, based on what we now know about MERS-CoV and SARS-CoV, neutralising antibodies that target additional spike protein regions should also exist [18]. Numerous studies have demonstrated the clinical safety and efficacy of antibody-based COVID-19 medications, which may lessen the strain on healthcare systems and economies during the pandemic [19, 20]. Key target populations for such monoclonal antibody therapy include individuals over 65 and immunocompromised patients, who are more vulnerable due to comorbidities [21]. Monoclonal antibodies that target the virus's spike protein are the subject of numerous research studies among the therapies that target SARS-CoV-2 [22, 23]. The impact of several SARS-CoV-2 mutations on the in vitro binding of clinically tested or authorised emergency use antibodies varies [24]. Mutations at amino acid residues 417, 439, 452, 484, and 501, respectively, had the greatest impact on how well antibodies and vaccines worked [11, 25]. Consequently, even in the presence of numerous mutations, recently created monoclonal antibodies ought to retain their potent neutralising activity.

A study examined the neutralising effects of several monoclonal antibodies against the Wuhan strain and the B.1.1.529 variation [26]. In line with the results published by Planas *et al.* [27], the majority of the neutralising mAbs showed a complete lack of neutralising activity. Sotrovimab and Evusheld (cilgavimab + tixagevimab) both demonstrated a decrease in neutralising activity against Omicron of less than two-fold and 100-fold, respectively, in comparison to the Wuhan strain [11, 26]. These results emphasise the necessity of creating neutralising monoclonal antibodies that target RBD epitopes with low mutation rates. The only neutralising monoclonal antibody that has been shown to have significant neutralising activity against the Omicron strain is bebtelovimab [11, 28]. Additionally, in a study published in December 2021, neutralisation testing was performed on various mAbs approved for clinical use in SARS-CoV-2-infected patients to evaluate their efficacy against Omicron [29]. All tested monoclonal antibodies lost their neutralising properties completely. However, Omicron was unaffected by any of the monoclonal antibody combinations that were examined [29].

It has been shown that bebtelovimab, a fully human IgG1 monoclonal SARS-CoV-2 antibody, neutralises all known VOCs of SARS-CoV-2, including Omicron and its subvariants (BA.2, BA.2.12.1, BA.4, and BA.5) [30]. Additionally, Bebtelovimab received an emergency use authorisation from the US FDA on February 11, 2022 [11, 30]. The alterations widely present in the newly identified variations, especially those that reduce the effectiveness of immunisations, differ significantly from the epitope that bebtelovimab binds to [30, 31]. Notably, amino acids rarely changed in the global GISAID EpiCoV database, facilitating the interaction between the S protein and bebtelovimab, indicating that bebtelovimab may offer a long-term solution for reducing COVID-19-related illness and mortality [11]. Even while bamlanivimab (LY-CoV555), another prospective neutralising antibody, demonstrated less powerful action than bebtelovimab [11], a recent investigation found that bebtelovimab successfully neutralised the virus [32]. Because of the rapid spread of the Omicron variation, which contains 35 mutations in the spike protein of the receptor binding domain, questions have been raised concerning the efficacy of various therapeutic monoclonal antibodies that have been tested commercially [33].

In pseudotyped neutralisation studies, the ability of various monoclonal antibodies to neutralise the Omicron variant was assessed; In these experiments, only bebtelovimab remained completely effective in combating the Omicron form [11]. Furthermore, the Omicron subvariant, BA.2, was neutralised, and it was discovered that bebtelovimab was still effective against this variant [11]. Even if bebtelovimab is widely distributed or spreads quickly, the figures show that it is still effective against VOCs. It appears that bebtelovimab may be particularly well-suited to fight the present variants because it has been demonstrated that many other efficient neutralising antibodies lose their capacity to neutralise a range of mutations [13]. Additionally, the changes in B.1.1.529, particularly G446S, N440K, Q498R, and N501Y, located within the binding epitope [34], did not influence the neutralizing activity of bebtelovimab. Particularly, bebtelovimab's robust efficiency against every variation tested indicates that it only binds to an epitope with slight alterations and is insensitive to evolving mutations. These results further imply that bebtelovimab is not only anticipated to maintain its potent neutralising action against existing variations but is also less likely to be impacted by upcoming changes due to the low level of mutational activity shown thus far in its binding epitope. Because of its unique binding epitope, this mAb may provide a therapeutic alternative against the Omicron variant and developing variations of COVID-19 in addition to vaccinations and currently available treatments.

Effects of melatonin on the immune system in COVID-19

Chronotherapy, sometimes referred to as circadian medicine or chronomedicine, seeks to treat patients during the optimal time of day to maximise health benefits and minimise negative effects [35]. Chronotherapy aims to optimise medicinal interventions while taking the circadian rhythms of the organism into account [35, 36]. Even slight biological clock dysfunction can have a big effect on sleep/wake physiology through raising diurnal somnolence, raising sleep onset latency, hindering or promoting the process of sleep onset, awakening frequently at night, reducing sleep efficiency, hindering and minimising rapid eye movement sleep, or raising periodic leg movements [36]. By regulating the clock, introducing planned light exposure, maintaining good sleep hygiene, and employing chronobiotic drugs like melatonin, which alter the output phase of circadian rhythms, chronotherapy seeks to restore the correct circadian pattern of the sleep-wake cycle [37]. 24-hour cycles of physiology and behaviour, including hormone release, metabolism, and sleep and wakefulness, are produced by biological time systems called circadian clocks [37]. As our knowledge of the molecular and cellular mechanisms underlying circadian physiology and disease advances, it is becoming practical to target circadian rhythms for sickness prevention and therapy.

Circadian rhythms and their impact on lung epithelial cells' vulnerability to SARS-CoV-2 infection were linked in a prior study [38]. According to this study, the primary viral receptor ACE2 was expressed less often, and virus entrance into lung epithelial cells was decreased when brain and muscle ARNT-like protein-1 (BMAL1), a crucial circadian transcriptional activator, was deleted. Reduced expression of the circadian rhythm-regulating BMAL1 gene triggers a series of events that result in cytokine storms through the NF-θB pathway, as was shown in COVID-19 [39]. In addition to the connection between the S protein and ACE2, it has been shown that SARS-CoV-2 directly interacts with cluster of differentiation 147 (CD147), a type I transmembrane protein implicated in viral infection [40]. Melatonin is a great therapy option to avoid severe COVID-19 symptoms because of its well-known anti-inflammatory, immunomodulatory, and antioxidant activities [41]. There is no direct antiviral effect of melatonin. It does, however, exhibit indirect antiviral qualities through anti-inflammatory, immunoprotective, and antioxidant effects [40, 41]. Additionally, it has been shown that melatonin controls blood levels of IFN-α and IL-2, two important players in the CD147-mediated inflammatory pathway, which lowers viral activity, acute lung injury, and virus-mediated stroke and mortality [40].

Melatonin offers considerable defence against oxidative cell damage and is a strong activator of antioxidant enzymes, including glutathione peroxidase and superoxide dismutase [42]. Melatonin provides a vital defence against oxidative cell damage by potently stimulating the antioxidant enzymes glutathione peroxidase and superoxide dismutase. Melatonin receptors (MT2) have also been discovered to be present in spleen cells [43]. External melatonin treatment has been demonstrated to promote spleen cell proliferation in rodents, such as mice, voles, and hamsters, with MT2 receptors being a key player in this stimulatory effect of melatonin [44]. Additionally, melatonin treatment promotes T cell proliferation [45]. Thymus gland function and T cell-mediated immunological responses in old mice are equal to those in young mice when melatonin is given to them. Melatonin promotes the production of T cell-mediated cytokines and reduces T cell death [45].

Acute respiratory distress syndrome (ARDS) and cytokine storm syndrome are brought on by COVID-19's unchecked inflammatory mediator production [46]. By increasing the activity of natural killer cells and decreasing reactive oxygen species, the interferon-gamma response, and T-helper cells, melatonin is believed to mitigate this cytokine storm [47]. To lessen the hyperinflammatory reaction to some respiratory infections, melatonin, like corticosteroids, decreases NF-B activation [40]. At greater doses, it also increases interleukin production [48]. These interleukins intensify the inflammatory reaction brought on by viral lung infections. A prior study found that melatonin reduced acute oxidative damage in the lungs by preventing the production of nitric oxide and malondialdehyde in mice infected with respiratory syncytial virus (RSV) [49].

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

Because the SARS-CoV-2 virus binds to ACE2 receptors to create cytokine storm and acute respiratory distress syndrome, oxidative reactions in the illness result in lung damage caused by reactive oxygen species (ROS) [50]. Reactive oxygen species are produced by viral infections. The immune system may be more susceptible to SARS-CoV-2 infection in older adults and those with serious co-morbidities like diabetes, cancer, and heart problems [47]. The development of COVID-19 infection is influenced by several variables, including weakened immune responses, the pathogenicity of new viral variations, and the unstable and uncontrollable creation of ROS associated with cytokine storms [50]. Reactive oxygen species and free metal ion production can be significantly

reduced by melatonin. Consequently, harmful effects like lipid peroxidation, protein oxidation, and DNA damage can be prevented [50].

Reactive oxygen species raise the expression of matrix metalloproteinase (MMP) [1]. Melatonin supplementation with ROS scavenging action can greatly reduce the harmful effects of excessive MMP synthesis [1, 40]. By lowering oxidative stress and cell death, melatonin may help reduce the pulmonary inflammation caused by COVID-19. Melatonin exhibits greater antioxidant activity than other well-known ROS scavengers, according to the studies [1]. Furthermore, the intensity of the inflammatory immune response is linked to the severity of the consequences caused by pro-inflammatory cytokines generated in the cytokine storm caused by SARS-CoV-2 infection [50]. Myeloperoxidase (MPO), a heme protein present in neutrophils, converts chloride (Cl-) to hypochlorous acid (HOCl) when H2O2 is present [42]. Strong oxidants like HOCl can have potent antibacterial effects under normal conditions [1]. HOCl, on the other hand, might prevent tissue damage when ROS production may increase uncontrollably under different inflammatory conditions [42]. The inflammatory immune response is strengthened by the significant impacts of MPO activity and ROS generation. MPO inhibition and the removal of undesirable ROS are crucial therapeutic targets for the treatment of SARS-CoV-2 infection [1]. Melatonin inhibits chlorination and allosteric interaction at the heme pocket entrance of the MPO enzyme [1, 40].

Due to its critical role in ROS detoxification, melatonin can also be regarded as a powerful boosting agent to fight the COVID-19 infection [40]. The COVID-19-induced cytokine storm encourages the MPO enzyme to become overactive. Excessive MPO activity is one of the main sources of HOCl, a major reactive oxygen species [42]. Therefore, lowering HOCl generation or metal release brought on by ROS, melatonin has a therapeutic impact on COVID-19. Additionally, it has been noted that melatonin increases the efficacy of various drugs used to treat COVID-19 while lowering the risk of side effects [1, 48]. In addition to COVID-19, melatonin significantly decreased circulating cytokine levels in other conditions with elevated inflammatory levels [47, 48]. Given all of this data, it has been shown that melatonin, even at large dosages, is safe for short-term use [48]. Therefore, as an adjuvant to vaccinations, melatonin supplements, which can rectify impaired circadian rhythms brought on by ageing and environmental factors, will successfully treat COVID-19. In light of this information, melatonin and bebtelovimab may be used as a safe therapeutic method for SARS-CoV-2 infection.

Conclusion

Vaccination is the best way to avoid COVID-19. Before or following exposure to the Omicron form, melatonin and bebtelovimab combination therapy can have a significant beneficial effect on the elderly and people with chronic illnesses. The greater contagiousness of the Omicron form has led to a rise in overall ER visits, hospital stays, and critical care unit admissions, despite its milder look. Omicron infections should therefore not be ignored, and the importance of vaccination should be emphasised, especially for high-risk persons. Finding and expanding therapeutic options is also essential, taking into account the cost and duration required to develop a vaccine that targets novel mutations. Bebtelovimab may be employed in clinical treatment, especially for patients with compromised immune systems, after being compared to the most common variations in independent clinical research and other therapeutic alternatives. Lastly, melatonin and bebtelovimab combination therapy may be a suitable approach as a vaccine adjuvant, with potential benefits to boost immunity and regulate circadian rhythm against Omicron and possible future variations of concern.

Acknowledgments: The author would like to thank the Near East University, Faculty of Pharmacy.

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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