Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Potential therapeutic role of budesonide to reduce COVID-19 severity

Coronavirus disease 2019 (COVID-19) has placed strain on the global health landscape. As of July 19, 2021, this emerging infection had caused 188,655,968 infections and 4,067,517 deaths [1]. Preliminary studies have reported that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) generally caused shortness of breath a few days after infection [2,3]. Therefore, shortness of breath is recognized as one of the hallmarks of COVID-19 infection [4]. Oxygen therapy has been reported to be beneficial for COVID-19 patients with breathing problems [5,6]. With the surge in COVID-19 patients, the demand for oxygen supply has increased several times. Oxygen shortages in hospitals have enlarged the complications of COVID-19, leading to an increase in the death rate. Therefore, it is urgent to study alternative therapies to reduce the severity of COVID-19. This study aimed to explore the therapeutic role of budesonide for lung diseases and elucidate the possible clinical implementation of budesonide in the reduction of COVID-19-related deaths.

Several corticosteroids have been studied regarding their effectiveness in treating COVID19 patients, such as dexamethasone, prednisone or methylprednisolone, and they have been found to be associated with a reduced risk of disease severity or death, while also preventing hospitalizations, and resulting in mild symptoms with minimal care required [7]. Some inhaled corticosteroids have been shown to disrupt SARS-CoV-2 viral replication while also negatively regulating the expression of receptors used for entry into cells [8]. These mechanisms support the potential of inhaled corticosteroids as therapeutic agents for COVID-19 patients.

Inhaled budesonide is a common corticosteroid used to treat asthma, chronic obstructive pulmonary disease (COPD) and bronchopulmonary dysplasia (BPD) [9–11]. Inhaled budesonide therapy has been reported to be able to replace oral corticosteroids in patients with severe asthma, thereby reducing the total corticosteroid dose and the risk of systemic side effects [12]. One study reported that once or twice daily doses of budesonide administered via the Turbuhaler and Pulmicort Respules systems was well tolerated and effective in populations with moderate to severe asthma [13]. Another study suggested that high-dose inhaled budesonide treatment may be effective in approximately 25% of COPD patients [14]. Another interesting study has shown that nebulized budesonide may be an effective and safe alternative to the use of systemic corticosteroids in the treatment of COPD exacerbations [15]. Yeh et al. found that in very low birth weight infants with severe respiratory distress syndrome, the intratracheal administration of surfactant/budesonide versus surfactant alone significantly reduced the incidence of BPD or death with no immediate adverse effects [16]. Du et al. stated that budesonide and Poractant Alpha prevent BPD by activating the SIRT1 signaling pathway [17]. Collectively, the above studies provide substantial support for the therapeutic role for budesonide in the treatment of asthma, COPD, and BPD.

A previous study found that among extremely premature infants, the incidence of bronchopulmonary dysplasia was lower among those who received inhaled budesonide early than among those who received placebo; however, the benefit may have been at the expense of higher mortality [11]. Another study indicated that nebulized budesonide (2 mg) could be given as an alternative to children who cannot tolerate oral dexamethasone [18]. Exposure to cold air or the administration of cold mist are therapeutic interventions for viral croup that are not supported by published evidence; however, breathing heliox can potentially reduce the work of breathing related to upper airway obstruction [18]. An interesting study reported that budesonide was associated with a decreased need for continuous mechanical ventilation, severe grade II bronchopulmonary dysplasia (BPD) or death (19−12%), grade III BPD or death (31−21%), and that the median gestational age at discharge was 1 week earlier [19].

In addition, one study stated that the intra-tracheal administration of the combination of budesonide and a surfactant was associated with a lower incidence of BPD alone or combined death or BPD in very low birth weight (VLBW) infants, although larger studies are needed before this can be recommended as a standard of care [20]. In very low birth weight infants with severe respiratory distress syndrome, the intratracheal administration of surfactant/budesonide versus surfactant alone significantly reduced the incidence of BPD or death with no immediate adverse effects [16]. Pavord et al. [21] reported that in patients with mild asthma, the effects of budesonide-formoterol as needed for exacerbations are independent of the biomarker profile, while the benefits of inhaled maintenance budesonide in patients with high eosinophil counts are greater than those in patients with a low eosinophil count. Hashemian et al. [22] stated that in chronic obstructive pulmonary disease (COPD) patients who received mechanical ventilation (MV), nebulized budesonide was associated with reduced levels of BAL CXCL8 and IL-6 and a reduced neutrophil count, as well as with improved ventilation mechanics, and that it facilitated weaning.

Moreover, Gudnadottir et al. [23] found that 6-week treatment with intranasal budesonide significantly improved the quality of life and symptoms in comparison to placebo nasal spray among

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children with sleep-disordered breathing. Kothe et al. [24] reported that budesonide reduced proinflammatory mRNA in the lung, liver and brain. Budesonide also reduced total protein and proinflammatory cytokines in bronchoalveolar lavage fluid (BALF) and reduced inducible nitric oxide synthase activation at 24 h. In ventilated premature lambs, most of the budesonide left the lung within 24 h. Adding budesonide to the surfactant improved physiology, reduced lung damage markers, and decreased systemic responses in the liver and brain. Kothe et al. [25] found that the surfactant budesonide matured the premature lungs and decreased the liver response but did not improve the lung function after high V_T injury in fetal sheep. Pan et al. [26] suggested that the intratracheal instillation of pulmonary surfactant (PS) combined with budesonide can effectively reduce the incidence of BPD in VLBW premature infants with severe neonatal respiratory distress syndrome (NRDS).

Furthermore, it has been reported that inhaled budesonide appears to offer an effective and safe alternative to oral steroids for the long-term maintenance treatment of patients with pulmonary sarcoidosis [27]. One study suggested that procaterol combined with budesonide was well tolerated and effective for improving cough symptoms and quality of life in patients with cough-variant asthma (CVA) [28]. Another study found that the curative effects in young children with an asthmatic variant of montelukast cough in combination with budesonide are significant [29]. Therapy was demonstrated to improve clinical symptoms and the lung function and reduce the serum levels of inflammatory factors in sick children, and was noted to have a high application value and to be worthy of application and promotion [29].

Nevertheless, a recent study reported that the early administration of inhaled budesonide reduced the likelihood of needing urgent medical attention and reduced recovery time after the onset of COVID-19 [30]. Results from previous in vitro studies suggest that SARS-CoV-2 replication is reduced in airway epithelial cells with the use of inhaled glucocorticoids [8]. Besides, inhaled glucocorticoids can lead to the downregulation of the expression of the angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2), both of which are essential for virus entry [8].

Inhaled budesonide has been studied in several small and large-scale outpatient studies for the treatment of patients with mild symptoms of COVID-19 [31]. The results of these trials suggest that in adult outpatients with mild COVID-19, the administration of inhaled budesonide may reduce the need for urgent care, emergency room assessments or hospitalization, while also reducing the recovery times [31]. In addition, the results of the PRINCIPLE trial, published in The Lancet on August 10, 2021, suggested that inhaled budesonide improves the recovery time and could potentially reduce hospital admissions or death [31]. A preprint report indicated that inhaled budesonide reduced the recovery times by an average of 3 days in people with COVID-19 with risk factors for adverse outcomes [32]. Another study suggested that early treatment with inhaled budesonide could prevent a clinical deterioration in COVID-19 patients [33].

Therefore, the above studies indicated that budesonide has a considerable therapeutic role in the treatment of shortness of breath and related pulmonary difficulties.

In conclusion, the death rate associated with the COVID-19 pandemic has increased to an unprecedented level. Lack of oxygen therapy is one of the factors responsible for the increase in deaths from COVID-19. Therefore, it is urgent to consider alternative treatments for COVID-19 patients when oxygen therapy is insufficient. A few recent studies reported the beneficial effects of budesonide in COVID-19 patients. Therefore, further preclinical and clinical studies are needed to clarify the fundamental role of budesonide in reducing COVID-19-related deaths.

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Author contributions

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Competing interest

The authors declare no conflicts of interest in association with the present study.

Informed consent

Not applicable.

Ethical approval

Not applicable.

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