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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Can roflumilast become steroid-sparing alternative in the treatment of COVID-19?

Chirag A. Shah

Community Welfare Foundation India, Sangli 416416, India

A B S T R A C T

According to WHO the worst of the COVID-19 pandemic is yet to come. Despite of the exceptional measures being undertaken by regulatory agencies to expedite vaccine development, we may be several months if not years away from an effective vaccine. In such unprecedented times, the only resort nations have at their disposal is to identify and repurpose existing drugs against COVID-19 based on their known clinical or pharmacological profile which can provide direct or corroborative evidence of favorable benefit: risk in the management of COVID-19. Immune-mediated inflammation remains the hallmark of severe complications related to COVID-19 and while corticosteroids have shown preliminary evidence of benefit, they can act like a double-edged sword for majority of COVID-19 patients. Therefore, there is a need to identify 'non-steroid' potent and safe anti-inflammatory agents for use in therapeutic armamentarium against COVID-19. This article makes a case for one such existing drug, roflumilast, that can emerge as a steroid-sparing alternative against COVID-19.

Background to hypothesis

Within months of its outbreak, the COVID-19 pandemic has infected millions of people, claimed thousands of lives and disrupted economies of virtually all nations. Originating from the family of zoonotic viruses known as Coronavirus, SARS-CoV-2 is responsible for causing COVID-19, a highly contagious disease [1]. Following the Severe Acute Respiratory Syndrome (SARS) and Middle-East Respiratory Syndrome (MERS), COVID-19 becomes the third zoonotic disease caused by coronaviruses affecting humans, albeit more ferocious in terms of spread with no clinically proven or specific antiviral agent available for treatment [2].

COVID-19 has a median incubation period of around 5 days. Clinical presentation of COVID-19 varies from asymptomatic disease to symptomatic presentation consisting of fever, sore throat, cough, loss of taste or smell, headache, diarrhea, shortness of breath. Acute respiratory distress syndrome (ARDS), septic shock, acute cardiac injury, renal injury with fatal outcomes have been reported in severe COVID-19 [3].

SARS-CoV-2 infection causes activation of innate and adaptive immune system. However, a combination of excess inflammatory innate response and overactive adaptive immune response leads to harmful tissue damage. In this regard, cytokine storm, a severe immune-inflammatory response resulting from the release of several pro-inflammatory cytokines, is often considered as a mechanism behind severe complications of COVID-19 such as ARDS or multi-organ failure [4].

Statement of hypothesis

Accumulating data clearly indicates that large amounts of pro-inflammatory mediators such as Interleukin (IL)-6, IL-12, IL-18, IL-33, Tumor necrosis factor α (TNFα), Interferon (IFN)-α, IFNγ, IL-1β and several chemokines (CXCL-2, 3, 5, 8, 9, 10), are responsible for triggering the cytokine storm, hallmark of COVID-19 related complications [5]. Amongst these, Interleukin-6 (IL-6) is believed to play important pathogenic role in cytokine storm [6]. Raised IL-6 levels positively correlate with disease severity in COVID-19 patients [5]. In animal models of SARS-CoV infection, the inhibition of IL-6 has been shown to have mortality benefits and several anti-IL-6 receptor antibodies are being tested in COVID-19 patients [7]. Similar to IL-6, TNF-α is an important cytokine that plays crucial role in COVID-19 inflammatory response [8]. Colony-stimulating factors enhance the cytokine production by immune cells that further enhances inflammatory reaction [9]. Chemokines are a group of cytokines secreted in viral infection and exert strong chemotactic effects. In animal models, anti-CXCL10 antibody has shown to attenuate lung injury, suggesting CXCL10 to be a critical chemokine in triggering ARDS. Similarly, raised levels of IL-8 in the circulation and in respiratory secretions of patients with ARDS can serve as a bio-marker to determine prognosis in COVID-19 patients [10].

Potent anti-inflammatory agents such as corticosteroids are being proposed to mitigate deleterious effects of cytokine storm in COVID-19 and many national treatment protocols have included such a recommendation [3,11]. The rationale behind corticosteroid use has been strengthened on the back of positive preliminary results from

E-mail address: chiirag@gmail.com.

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RECOVERY trial [12] that showed use of dexamethasone led to lower mortality rate in hospitalized COVID-19 patients. However, it must be noted that steroids in viral infections can behave like a double-edged sword. e.g. corticosteroid therapy led to attenuation of viral clearance in SARS, MERS, influenza and appears to worsen clinical outcomes and increases propensity of bacterial infections and mortality [3]. As a result benefit:risk ratio of corticosteroids may not be uniform across varying disease severity of COVID-19 and their generalized use may cause more harm than benefits. Therefore, exploring 'non-steroid' agents that demonstrate desirable anti-inflammatory properties to mitigate cytokine storm but that are devoid of steroid related safely concerns is need of an hour in the fight against COVID-19.

In this context roflumilast, a Phosphodiesterase 4 (PDE4) inhibitor, deserves attention. PDE4 regulates pro-inflammatory cytokines and serves as an important modulator of airway inflammation. Inhibition of PDE4 causes cAMP accumulation which leads to favorable immune-modulating effects [13,14].

Need to test the hypothesis

Roflumilast is an orally administered PDE4 inhibitor approved in the EU, US and several countries in the world for treatment of chronic-obstructive pulmonary disease (COPD). Abnormal immune response and severe respiratory inflammation are characteristics of COPD. Preclinical pharmacological studies demonstrate potent anti-inflammatory and immuo-modulatory effects of roflumilast. e.g. roflumilast potently inhibits PDE4 in neutrophils, macrophages, monocytes, dendritic cells, CD4+ and CD8+ T cells leading to anti-inflammatory effects, suppression of pro-inflammatory mediators, TNF-α synthesis and inhibition of cytokine production [15].

Roflumilast has shown to cause inhibition of major airway pro-inflammatory markers such as IL-4, IL-5, IL-6, IL-13, IL-17, IL-8, granulocyte-macrophage colony stimulating factor (GM-CSF) with reduction in levels of IL-1β, CCL-2, 3, 4 and CXCL10. Elevated cAMP due to roflumilast leads to reduced secretion of TNF- α and IL-12 by dendritic cells and increase level of anti-inflammatory cytokine (IL-10) to produce an overall potent and balanced anti-inflammatory effect [13]. Beneficial effects of roflumilast in terms of reduction in hypoxia [16], cytokine production and prevention of lung infiltration by immune cells have been demonstrated in animal models [17].

In-vivo data comparing roflumilast versus dexamethasone shows that unlike dexamethasone that non-specifically inhibits numerous mediators involved in inflammation and the immune response, roflumilast selectively inhibits a subset of pro-inflammatory mediators and growth factors [18]. Roflumilast has also shown to be useful in severe asthma exacerbations due to viral infections that cannot be sufficiently controlled by corticosteroids such as dexamethasone or fluticasone [19]. COPD patients with pronounced inflammation and advanced disease have shown better reduction in exacerbation risk observed with roflumilast in clinical studies [20]. Based on preliminary screening and prediction for anti-viral activity, a signal of possible anti-viral activity of roflumilast against SARS-CoV-2 cannot be ruled out [21].

Based on its established benefit:risk ratio in treatment of lung disorders and known mechanistic and pharmacological profile providing corroborative evidence of likely benefits in suppressing mediators involved in cytokine storm, there is adequate rationale to test whether roflumilast will emerge as a beneficial anti-inflammatory or immune modulating agent in the management of patients with COVID-19.

Compared to another PDE4 inhibitor apremilast (which is approved for treatment of psoriasis) [22], roflumilast has a long elimination half-life, convenient once daily dosing that does not require complex titration, reduced incidence of gastro-intestinal side-effects and close to a decade of clinical experience in management of inflammatory lung disorders such as COPD. Therefore, roflumilast is an ideal PDE4 inhibitor to be investigated further as a 'steroid-sparing' alternative in the treatment of patients with COVID-19.

Conclusion

Roflumilast may prove to be an important steroid-sparing anti-inflammatory agent in managing COVID-19 related immune-inflammatory manifestations and complications. Clinical trials to explore roflumilast as a monotherapy or in combination paradigm with standard of care or antivirals are hence warranted to establish place of this existing and safe drug in the treatment of patients across COVID-19 severity spectrum.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110246.

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