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Commentary: Phosphodiesterase 4 inhibitors as potential adjunct treatment targeting the cytokine storm in COVID-19

Maria Dalamaga [a,*,1], Irene Karampela [a,b,1], Christos S. Mantzoros [c]

[a] Department of Biological Chemistry, School of Medicine, National and Kapodistrian University of Athens, 75 Mikras Asias Street, 11527 Athens, Greece
[b] Second Department of Critical Care, Attikon General University Hospital, Medical School, National and Kapodistrian University of Athens, Chaidari, Greece
[c] Section of Endocrinology, Boston VA Healthcare System, Harvard Medical School, Boston, MA, USA

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ABSTRACT

The most severe presentation of COVID-19 is characterized by a hyperinflammatory state attributed to the massive pro-inflammatory cytokine release, called "cytokine storm". Several specific anti-inflammatory/immunosuppressive agents are being evaluated by ongoing clinical trials; however, there is currently insufficient evidence for their efficacy and safety in COVID-19 treatment. Given the role of phosphodiesterase 4 (PDE) 4 and cyclic adenosine monophosphate in the inflammatory response, we hypothesize that selective PDE4 inhibition may attenuate the cytokine storm in COVID-19, through the upstream inhibition of pro-inflammatory molecules, particularly TNF-α, and the regulation of the pro-inflammatory/anti-inflammatory balance. Conversely, other anti-cytokine agents lead to the downstream inhibition of specific targets, such as IL-1, IL-6 or TNF-α, and may not be efficient in blocking the cytokine storm, once it has been triggered. Due to their mechanism of action targeting an early stage of the inflammatory response and ameliorating lung inflammation, we believe that selective PDE4 inhibitors may represent a promising treatment option for the early phase of COVID-19 pneumonia before the cytokine storm and severe multiorgan dysfunction take place. Furthermore, PDE4 inhibitors present several advantages including an excellent safety profile; the oral route of administration; the convenient dosing; and beneficial metabolic properties. Interestingly, obesity and diabetes mellitus type 2 have been reported to be risk factors for the severity of COVID-19. Therefore, randomized clinical trials of PDE4 inhibitors are necessary to explore their potential therapeutic effect as an adjunct to supportive measures and other therapeutic regiments.

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic posed an unprecedented threat to public health globally due to the high morbidity and mortality of the coronavirus disease 2019 (COVID-19) [1,2]. The clinical manifestations of COVID-19 range from very mild symptoms to life-threatening organ dysfunction and death [3]. The most severe presentation of COVID-19 is characterized by a hyperinflammatory state, attributed to the massive pro-inflammatory cytokine release, called "cytokine storm" [4]. The induction of pro-inflammatory cytokines by the SARS-CoV-2 triggers an auto-amplifying inflammatory cascade involving multiple pathways and resulting in severe organ damage such as acute respiratory distress syndrome (ARDS) [3,4]. The immune response to SARS-CoV-2 infection has been shown to be analogous to the clinical presentation and the severity of the disease [5].

Preliminary studies have indicated that immune cell populations such as lymphocyte subsets (CD4+, CD8+ and NK cells) are reduced while cytokines are upregulated during severe COVID-19 pneumonia [6–9]. Thus, early inhibition of inflammatory pathways represents an attractive therapeutic approach [5,10]. This is the basis for the investigational use of specific anti-inflammatory/immunosuppressive agents in the treatment of COVID-19, such as interleukin (IL)-6 receptor antagonist monoclonal antibodies (tocilizumab, sarilumab), IL-6 inhibitors (siltuximab), IL-1 inhibitors (anakinra), tumor necrosis factor (TNF-α) inhibitors (adalimumab) and the Janus kinase inhibitors (febratinib, baricitinib) [11,12]. As these agents are being evaluated by ongoing clinical trials, there is currently insufficient evidence for their efficacy and safety in COVID-19 treatment [13–15]. Furthermore, these agents are potent immunosuppressives; thus, there are justified fears of potential

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; cAMP, cyclic adenosine monophosphate; COPD, chronic obstructive pulmonary disease; COVID-19, Coronavirus Disease 2019; HIV, Human Immunodeficiency Virus; IFN, Interferon; IL, interleukin; NF-kB, Nuclear Factor kB; NK, Natural Killer cell; PDE4, phosphodiesterase 4; PKA, protein kinase A; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; TNF-α, Tumor Necrosis Factor-α.

* Corresponding author at: Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, 75 Mikras Asias street, 11527 Athens, Greece.
E-mail address: madalamaga@med.uoa.gr (M. Dalamaga).
[1] These authors have contributed equally to this manuscript.

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detrimental rather than beneficial effects of impairment of immunity on severely affected patients [16]. However, there is evidence suggesting that patients on chronic anti-cytokine treatment for immune-mediated inflammatory diseases are not at a higher risk for worse outcomes from COVID-19 [17].

Among the multiple molecular pathways involved in the inflammatory response, cyclic adenosine monophosphate (cAMP), a potent intracellular second messenger, holds a key role in modulating cytokine release through protein kinase A (PKA) and the nuclear factor kB (NF-κB) pathway, resulting in the suppression of major pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), and the induction of the anti-inflammatory IL-10 [18]. The intracellular levels of cAMP in inflammatory cells are dependent on the activity of phosphodiesterase 4 (PDE4), an enzyme responsible for the cleavage of cAMP [19]. The inhibition of PDE4 results in multiple anti-inflammatory effects in a wide range of cells (macrophages, neutrophils, monocytes, T and B lymphocytes, dendritic and epithelial cells) due to the wide distribution of the PDE4 expression [20]. The resulting accumulation of intracellular cAMP and the subsequent activation of protein kinase A (PKA) inhibit inflammatory responses of macrophages (downregulation of TNFα and IL-12; upregulation of IL-10), dendritic cells (inhibition of antigen presentation), T-helper cells (downregulation of Th1 proliferation and release of IFNγ, IL-2, IL-4, IL-13, IL-17 and IL-22), B cells (attenuation of antibody production) and epithelial cells (downregulation of inflammatory mediators and enhancement of barrier integrity) [20,21]. Thus, PDE4 modulates both the innate and adaptive immune response affecting multiple inflammatory cells and the epithelium, while it also regulates both pro- and anti-inflammatory cytokine productions by fine tuning the intracellular cAMP levels [19,20].

The inhibition of PDE4 has been an effective therapeutic target for many inflammatory diseases such as asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, psoriasis and atopic dermatitis [20–22]. There is evidence that PDE4 expression is higher in patients suffering from inflammatory diseases compared to healthy subjects [23]. Selective PDE4 inhibitors have been shown to effectively inhibit pro-inflammatory cytokines (TNFα, IFNγ, IL-2, IL-12, IL-17 and IL-23) in inflammatory cells both *in vitro* and *in vivo*, and suppress the production of reactive oxygen species [20,21,24]. Interestingly, IL-17, the major inflammatory cytokine produced by type-17 T-helper cells, has been implicated in acute lung injury caused by respiratory viral infections including influenza and COVID-19 [8,25]. IL-17 neutralization has been demonstrated to ameliorate acute lung injury caused by influenza A H1N1 virus in mice [26]. Thus, targeting IL-17 has been proposed as a potential treatment for combating acute lung injury caused by SARS-CoV-2 [27]. Furthermore, PDE4 inhibition has been shown to attenuate pulmonary fibrin deposition and vascular alveolar leakage, and prolong survival in an animal model of hyperoxia-induced lung injury, as well as reduce lung fibrosis in animal models of lung injury [28,29]. These beneficial effects may have important therapeutic implications in COVID-19 pneumonia, which, when severe, may result in acute lung injury and lung fibrosis [30,31].

Currently, two orally administered PDE4 inhibitors, roflumilast and apremilast, have been approved for the treatment of inflammatory airway and skin diseases [20]. Apremilast is used for the treatment of moderate and severe psoriasis, psoriatic arthritis, and oral ulcers in Behçet's syndrome, while it has been also investigated in rheumatoid arthritis, ankylosing spondylitis, atopic dermatitis and inflammatory bowel disease among others [20–22,32–34]. Roflumilast is primarily used for the prevention of exacerbations of severe COPD associated with chronic bronchitis [35]. Moreover, crisaborole, another PDE4 inhibitor, was approved in the USA for the topical treatment of mild-to-moderate atopic dermatitis in patients aged 2 years and older [20]. In addition to these three PDE4 inhibitors, a series of novel PDE4 inhibitors have been designed to regulate the therapeutic efficacy by minimizing the adverse effects such as gastrointestinal reactions, nausea, emesis, loss of appetite, minor weight loss and headache. Novel PDE4 inhibitors, such as ronomilast, revamilast, cilomilast, tetomilast, oglemilast, GSK256066, CHF6001, YM976, GS-5759, *etc*., have been developed for the treatment of inflammatory airway and bowel diseases as well as autoimmune disorders [20].

We speculate that PDE4 inhibitors may be a valuable therapeutic option to COVID-19 treatment due to their unique mechanism of action, resulting to the upstream inhibition of multiple cytokine signaling pathways along with the regulation of the pro-inflammatory/anti-inflammatory balance. Conversely, other anti-cytokine agents lead to the downstream inhibition of specific targets, such as IL-1, IL-6 or TNF-α, and may not be efficient in blocking the cytokine storm, once it has been triggered. Furthermore, PDE4 inhibitors may specifically ameliorate airway and lung inflammation, and protect patients from COVID-19 associated acute lung injury and severe respiratory failure leading to intubation and high mortality. Moreover, apremilast has an excellent safety profile, as it has been shown to be associated with a significantly lower risk for serious and opportunistic infections compared to other immunosuppressive agents in patients with psoriasis and psoriatic arthritis as well as in immunosuppressed HIV patients [36]. Additional advantages of PDE4 inhibitors comprise the oral route of administration and the convenient dosing [33].

Noteworthy, apremilast presents beneficial metabolic properties by reducing body weight, enhancing lipolysis, increasing insulin sensitivity and reducing the accumulation of adipose tissue in the liver, especially in patients with high glycated haemoglobin and obesity [22,37,38]. Interestingly, obesity and diabetes mellitus type 2 have been reported to be risk factors for the severity of COVID-19 [1]. Furthermore, severe obesity has been shown to be independently associated with in-hospital mortality of COVID-19 [39]. Obesity is characterized by a chronic low-grade systemic inflammatory state with increased expression of pro-inflammatory cytokines. This pre-existing state of hyperinflammation may be responsible for the augmented inflammatory response to acute infection with SARS-CoV-2 (cytokine storm), representing the missing link between obesity and severity, and mortality of COVID-19 [40]. It is reasonable to assume that anti-inflammatory properties of PDE4 inhibitors may attenuate the severity of the cytokine storm in the context of the pro-inflammatory milieu due to obesity.

Given the role of PDE4 and cAMP in the inflammatory response, we hypothesize that selective PDE4 inhibition may attenuate the cytokine storm in COVID-19, through the upstream inhibition of pro-inflammatory molecules. In a recent COVID-19 case report, a patient receiving apremilast for severe psoriasis recovered successfully from COVID-19 with no adverse effects, suggesting that the anti-inflammatory properties of apremilast may present a beneficial effect in the SARS-CoV-2 infection [41].

Due to the mechanism of action targeting an early stage of the inflammatory response, we believe that selective PDE4 inhibitors may represent an attractive and promising treatment option for the early phase of COVID-19 pneumonia before the cytokine storm and severe multiorgan dysfunction take place. At present, there is no effective specific treatment for COVID-19 with the exception of preliminary evidence from remdesivir trials [42,43]. Therefore, proof of concept studies in patients with COVID-19 as well as randomized clinical trials of PDE4 inhibitors are necessary to explore their potential therapeutic effect as an adjunct to supportive measures and other therapeutic regiments.

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Author contributions

Maria Dalamaga conceived the idea, designed the commentary, performed literature search, wrote some parts of the manuscript, edited and reviewed the manuscript.

Irene Karampela performed literature search, wrote, edited and reviewed the manuscript.

Christos S Mantzoros supervised, edited and reviewed the manuscript.

Declaration of competing interest

No conflict of interest to disclose.

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