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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Commentary: Phosphodiesterase 4 inhibitors as potential adjunct treatment targeting the cytokine storm in COVID-19

Maria Dalamaga a,⁎, 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

ARTICLE INFO

Article history:
Received 15 May 2020
Accepted 30 May 2020

Keywords:
Apremilast
Coronavirus
Cytokine storm
COVID-19
Cyclic adenosine monophosphate
Phosphodiesterase 4 inhibitor
Pneumonia
Psoriasis
Rofufulast

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 regimens.

⁎ These authors have contributed equally to this manuscript.
inhibitors have been designed to regulate the therapeutic ef-
cacy by minimizing the adverse effects such as gastrointestinal reactions, nau-
sea, emesis, loss of appetite, minor weight loss and headache. Novel
PDE4 inhibitors, such as rononilast, revamilast, cilomilast, tetomilast, ogremlast, 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 op-
tion to COVID-19 treatment due to their unique mechanism of action,
resulting in the upstream inhibition of multiple cytokine signaling path-
ways 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 amelio-
rate 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 expres-
sion of pro-inflammatory cytokines. This pre-existing state of
hyperinflammation may be responsible for the augmented inflamma-
tory response to acute infection with SARS-CoV-2 (cytokine storm),
representing the missing link between obesity and severity, and mortal-
ity 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 pa-
tient 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 benefi-
cial 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 spe-
cific treatment for COVID-19 with the exception of preliminary evi-
dence 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.

Financial support

None.

Author contributions

Maria Dalamaga conceived the idea, designed the commentary, per-
formed 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.

References

[1] Richardson S, Hirsch J, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. Apr 22, 2020. https://doi.org/10.1001/jama.2020.6775.

[2] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu Q, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475–81. https://doi.org/10.1016/S2213-2600(20)30079-5.

[3] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. Mar 13, 2020. https://doi.org/10.1001/jamainternmed.2020.0994.

[4] Ye Q, Wang R, Mao J. The pathogenesis and treatment of the 'cytokine Storm' in COVID-19. J Infect. 2020. https://doi.org/10.1016/j.jinf.2020.03.017. Apr 10. 50163-4453/20.30165-1.

[5] Ingraham NE, Loft-Ernæn S, Thielken BK, Techar K, Morris RS, Holtan SG, et al. Immunomodulation in COVID-19. Lancet Respir Med. 2020. https://doi.org/10.1016/S2213-2600(20)30226-5. May 4. S2213-2600(20)30226-5.

[6] Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). medRxiv. 2020. https://doi.org/10.1101/2020.02.02.20021832 [preprint].

[7] Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620–9. https://doi.org/10.1172/jci131724.

[8] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019-nCoV in Wuhan, China. Lancet. 2020;395(10223):497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

[9] Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323(16):1574–81. https://doi.org/10.1001/jama.2020.5394.

[10] Pan Y, Guan H, Zhou S, et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV), a study of 63 patients in Wuhan, China. Eur Radiol. 2020;30(6):3306–9. https://doi.org/10.1007/s00330-020-06731-x.

[11] Chiricozzi A, Caposiena D, Carafa C, Cannello MV, Chimenti S, Saraceno R. A new therapeutic for the treatment of moderate to severe plaque psoriasis: apremilast. Expert Rev Clin Immunol. 2016;12(12):237–49. https://doi.org/10.1586/1744666X.2016.1134319.

[12] Torres T, Puig L, Apremilast: a novel oral treatment for psoriasis and psoriatic arthritis. Am J Clin Dermatol. 2018;19(1):23–32. https://doi.org/10.1007/s40257-017-0302-0.

[13] Hatermi C, Mahr A, Ishigatsubo Y, Song YW, Takeno M, Kim D, et al. Trial of apremilast for oral ulcers in Behcet’s syndrome. N Engl J Med. 2019;381(20):1918–28. https://doi.org/10.1056/NEJMoa2007764.

[14] Martinez FJ, Calverley PM, Goehring UM, Brote M, Fabbri LM, Rabe KF. Effect of rolUFILIN on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. Lancet. 2015;385(9971):857–66. https://doi.org/10.1016/S0140-6736(14)62410-7.

[15] Paroutoglou K, Papadavid E, Christodoulatos GS, Dalamaga M. Deciphering the association between psoriasis and obesity: current evidence and treatment considerations. Curr Obes Rep. 2020 May 16. https://doi.org/10.1007/s13679-020-00380-3.

[16] Armesto S, González Vela C, González López MA. Opportunistic virus infections in inflammatory diseases: effects of apremilast in psoriatic blood and in dermal myofibroblasts through the PDE4/C217 complex. Cell. 2016;26(7):753–63. https://doi.org/10.1016/j.jceld.2016.01.007.

[17] Schafar PH, Parton A, Gandhi AK, Capone L, Adams M, Wu L, et al. Apremilast, a cAMP pathway-activating inhibitor in patients with rheumatoid arthritis. Biochem Pharmacol. 2012;83(12):1583–91. https://doi.org/10.1016/j.bcp.2012.02.020.

[18] Crowe CR, Chen K, Pociask DA. Critical role of IL-17RA in immunopathology of inflammatory diseases. Front Immunol. 2016;7:123. https://doi.org/10.3389/fimmu.2016.00123.

[19] Dalamaga M, Karampela, Mantzoros CS. Commentary: could iron chelators prove to be useful as an adjunct to COVID-19 treatment regimens? Metabolism. 2020 Jul;108:154260.