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.

Metabolism Clinical and Experimental 110 (2020) 154300

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

COVID-19 in Metabolism

Letter to the editor: Immunomodulation by phosphodiesterase-4 inhibitor in COVID-19 patients

To the Editor,

We read with interest the commentary by Dalamaga and colleagues [1] that brought to the attention of the scientific community the potential role of Phosphodiesterase 4 (PDE4) inhibitors in the treatment of SARS-CoV-2 infection. Coronavirus disease 2019 (COVID-19) is associated with a variable clinical picture, ranging from mild "flu-like" cases to severe interstitial pneumonia leading to fatal respiratory insufficiency. This heterogeneity is attributed to the degree of the host's inflammatory reaction and cytokine production [2]. In the commentary it was suggested that Phosphodiesterase 4 (PDE4) could be a potential target of immunomodulation during the early phases of SARS-CoV-2 pneumonia, ideally preventing the overproduction of cytokines that characterizes the more severe forms of COVID-19 [3]. PDE4 regulates the balance between pro- and anti-inflammatory mediators and its inhibition dampens multiple cytokine signalling pathways allowing the restoration of the homeostatic cellular state [4]. In animal model PDE4 inhibitors prevented carfilzomib-induced lung injury via the inhibition of TNF-α and NF-κB activation suggesting a potential efficacy in inflammatory-mediated pneumonia [5]. Most noticeably, previous reports indicate that PDE4 inhibitors can safely be used in patients with chronic viral infection [6–8]. The safety profile of PDE4 inhibitors in SARS-CoV-2 infection is documented in a report describing a patient with psoriasis and COVID-19 who did not discontinued treatment with Apremilast (oral PDE4-inhibitors) with a rapid and positive outcome [9].

Herein, we describe, for the first time, four cases of SARS-CoV-2 related pneumonia successfully treated with Apremilast. All the patients had a confirmed SARS-CoV-2 infection by nasopharyngeal swab and a severe lung involvement, defined as respiratory rate ≥30 breaths/min OR oxygen saturation ≤93% at rest OR PaO_2/inspired oxygen fraction <300 mmHg AND/OR lung infiltrates ≥50% on chest x-rays [2]. The patients' clinical characteristics and main indication for Apremilast use are reported in the Table 1. Apremilast was given at the dose of 30 mg bid for 14 days (without titration) on compassionate use and after

Table 1
clinical and demographic characteristics

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	29	84	57	80
Sex	M	M	M	F
Medical history	HBV infection	Hypertension, nephrectomy for renal cancer, *benign prostatic hyperplasia*	Hypertension, psoriasis	Hypertension, prosthetic mitral valve, atrial fibrillation
Home therapy	None	Beta-blockers, Finasteride	Calcium-channel blockers, angiotensin receptor blockers	Beta-blockers, Acenocoumarol
Symptoms at admission	12-days fever, dry cough, dyspnoea	14-days fever, dry cough, dyspnoea	11-days dry cough, vomiting, 4-days fever, dyspnoea	2-days fever, dyspnoea
p/f, mmHg at room air	342	267	362	250
Respiratory rate at room air	30	24	32	24
Extent lung involvement, %	50	70	40	60
Lymphocytes, cells/μL	1590 - 2680***	870 - 920***	1114 - 1290***	880 - 970***
CRP, mg/dL	4.8 - 0.59***	7.7 - 2.6***	9.75 - 0.83***	8.2 - 1.8***
Ferritin, μg/L	2960 - 898***	843 - 475***	1222 - 800***	503 - 471***
Fibrinogen, mg/dL	626 - 481***	567 - 410***	567 - 459***	459 - 337***
D-Dimer, μg/L	4800 - 1870***	13189 - 4570***	500 - 203***	694 - 782***
IL-6, ng/L	21 - 2.5*	60 - 33**	37.2 - 3.5*	67 - 29**
Therapy from hospitalization	Hydroxychloroquine 200 mg bid; enoxaparin 4000 IU/day; O_2 therapy (up to FiO_2 28%)	Hydroxychloroquine 200 mg bid; enoxaparin 4000 IU/day; azythromycin 500 mg/day; ceftriaxone 2 g/day; O_2 therapy (up to FiO_2 40%)	Hydroxychloroquine 200 mg bid; Enoxaparin 4000 IU/day; azythromycin 500 mg/day; ceftriaxone 2 g/day; O_2 therapy (up to FiO_2 28%)	Hydroxychloroquine 200 mg bid; enoxaparin 4000 IU/day; azythromycin 500 mg/day; ceftriaxone 2 g/day; O_2 therapy (up to FiO_2 35%)
Hospitalisation before Apremilast, days	4	8	6	7
Main indication for Apremilast therapy	Persistent fever and tachypnea	Increased oxygen requirements	Persistence fever, fatigue, severe myalgia and tachypnea	Persistent fever, increased oxygen requirements
Outcome	Discharge after 5 days of Apremilast therapy	Discharge after 7 days of Apremilast therapy	Discharge after 5 days of Apremilast therapy	Discharge after 12 days of Apremilast therapy
Negative swab after discharge, days	21	14	28	21

p/f, PaO_2 to inspired oxygen fraction FiO_2 rate; Extent lung involvement on chest x-rays; CRP, C-reactive protein; values at admission and (***) after therapy with Apremilast; IL-6, interleukin 6 as measured before and after *5 days or **7 days of therapy with Apremilast. Discharge criteria: absence of fever for 3 days and SaO_2 ≥ 94% and RR < 24 at rest at room air and resolution of constitutional symptoms.

https://doi.org/10.1016/j.metabol.2020.154300

signing informed consent about the off-label nature of the treatment. Apremilast rapidly led to defervescence and to the improvement of gas exchanges in those otherwise unresponsive to supportive therapy. Treatment was well tolerated and only one patient developed mild and self-limiting diarrhoea.

In conclusion, we provide initial evidence that Apremilast is safe and beneficial in SARS-CoV-2 pneumonia also in patients with negative prognostic factors, such as older age, cardio-vascular comorbidities, lower lymphocyte count, greater extent of lung involvement and higher IL-6 levels. Our experience supports the use of PDE4-inhibitors in SARS-CoV-2 pneumonia as hypothesised by Dalamaga and colleagues [1]. Further studies are however needed to confirm these findings and to identify the patients would most benefit from this treatment.

Author contribution statement

AS, BV and LB all contributed to the conceptual design, drafting and revision of the manuscript and to the collection of data.

Declaration of competing interest

The authors declare no conflict of interest.

References

[1] Dalamaga M, Karampela I, Mantzoros CS. Commentary: phosphodiesterase 4 inhibitors as potential adjunct treatment targeting the cytokine storm in COVID-19 [published online ahead of print, 2020 Jun 1]. Metabolism. 2020;109:154282. https://doi.org/10.1016/j.metabol.2020.154282.

[2] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. [published online ahead of print, 2020 Feb 24] JAMA. 2020. https://doi.org/10.1001/jama.2020.2648.

[3] Tay MZ, Poh CM, Rénia L, MacAry PA, LFP Ng. The trinity of COVID-19: immunity, inflammation and intervention. [published online ahead of print, 2020 Apr 28] Nat Rev Immunol. 2020:12. https://doi.org/10.1038/s41577-020-0311-8.

[4] Schafer PH, Parton A, Gandhi AK, et al. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. Br J Pharmacol. 2010;159(4):842–55. https://doi.org/10.1111/j.1476-5381.2009.00559.x.

[5] Imam F, Al-Harbi NO, Al-Harbi MM, et al. Apremilast ameliorates carfilzomib-induced pulmonary inflammation and vascular injuries. Int Immunopharmacol. 2019;66:260–6. https://doi.org/10.1016/j.intimp.2018.11.023.

[6] Reddy SP, Shah VV, Wu JJ. Apremilast for a psoriasis patient with HIV and hepatitis C. J Eur Acad Dermatol Venereol. 2017;31:e481–2. https://doi.org/10.1111/jdv.14301.

[7] Manfreda V, Esposito M, Campione E, Bianchi L, Giunta A. Apremilast efficacy and safety in a psoriatic arthritis patient affected by HIV and HBV virus infections. Postgrad Med. 2019;131:239–40. https://doi.org/10.1080/00325481.2019.1575613.

[8] Boulougoura A, Gabriel E, Laidlaw E, et al. A phase I, randomized, controlled clinical study of CC-11050 in people living with HIV with suppressed plasma viremia on antiretroviral therapy (APHRODITE). Open Forum Infect Dis. 2019;6:ofz246. https://doi.org/10.1093/ofid/ofz246.

[9] Mugheddu C, Pizzatti L, Sanna S, Atzori L, Rongioletti F. COVID-19 pulmonary infection in erythrodermic psoriatic patient with oligodendroglioma: safety and compatibility of apremilast with critical intensive care management. J Eur Acad Dermatol Venereol. 2020. https://doi.org/10.1111/jdv.16625 May 9.

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19 June 2020