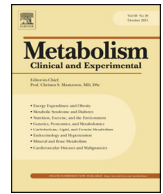




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COVID-19 in Metabolism

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- κ B 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 $\leq 93\%$ at rest OR PaO₂/inspired oxygen fraction < 300 mmHg AND/OR lung infiltrates $\geq 50\%$ 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/ μ L	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, μ g/L	2960 - 898***	843 - 475***	1222 - 800***	503 - 471***
Fibrinogen, mg/dL	626 - 481***	567 - 410***	567 - 459***	459 - 337***
D-Dimer, μ g/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, PaO₂ to inspired oxygen fraction FiO₂ 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 SaO₂ $\geq 94\%$ and RR < 24 at rest at room air and resolution of constitutional symptoms.

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.

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