


## COMMENTARY

# A European pharmacotherapeutic agent roflumilast exploring integrated preclinical and clinical evidence for SARS CoV-2 mediated inflammation to organ damage

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COVID-19 has spread globally, affecting almost 160 million individuals. Elderly and pre-existing patients (such as diabetes, heart disease and asthma) seem more susceptible to severe illness with COVID-19. Roflumilast was licensed for usage in the European Union in July 2010 as a phosphodiesterase-4 (PDE4) inhibitor. Under pre-clinical studies, roflumilast has been shown to decrease bleomycin-induced lung fibrosis, lung hydroxyproline and right heart thickening. The current study reviewed existing data that the PDE-4 inhibitor, a roflumilast, protects renal tissues and other major organ systems after COVID-19 infection by decreasing immune cell infiltration. These immune-balancing effects of roflumilast were related to a decrease in oxidative and inflammatory burden, caspase-3 suppression and increased protein kinase A (PKA)/cyclic A.M.P. (cAMP) levels in renal and other organ tissue.

## KEYWORDS

COVID-19, kidney injury, PDE-4 inhibitor, Roflumilast, tumour necrosis factor-alpha

## 1 | INTRODUCTION

COVID-19 has spread worldwide, causing about 332 001 132 verified cases and 5 565 957 deaths in people. COVID-19 appears to be particularly dangerous to the elderly and those with pre-existing conditions (such as diabetes, cardiovascular diseases and asthma). Diabetic

patients who become infected might be challenging to treat due to increases in blood glucose and other diabetes-related problems. Significant comorbidity towards SARS CoV-2-related COVID-19 includes inflammatory cytokine storm, acute kidney injury, myocarditis, thrombosis, acute respiratory distress syndrome (ARDS) and transient ischemic attack (T.I.A.) mediated cerebral complication that ultimately leads

to multi-organ failure. A new case report depicts a middle-aged man's unique initial presentation and subsequent problems. The person complained of abdominal discomfort and vomiting then was diagnosed with severe acute renal damage. The study participant had a myocardial infarction and respiratory failure while in the hospital. This indicates that this patient most likely developed cardiorenal syndrome due to COVID-19-associated acute renal injury.<sup>1</sup> Notably, the main contributor to the aforementioned consequences of organ damage and death is inflammation.

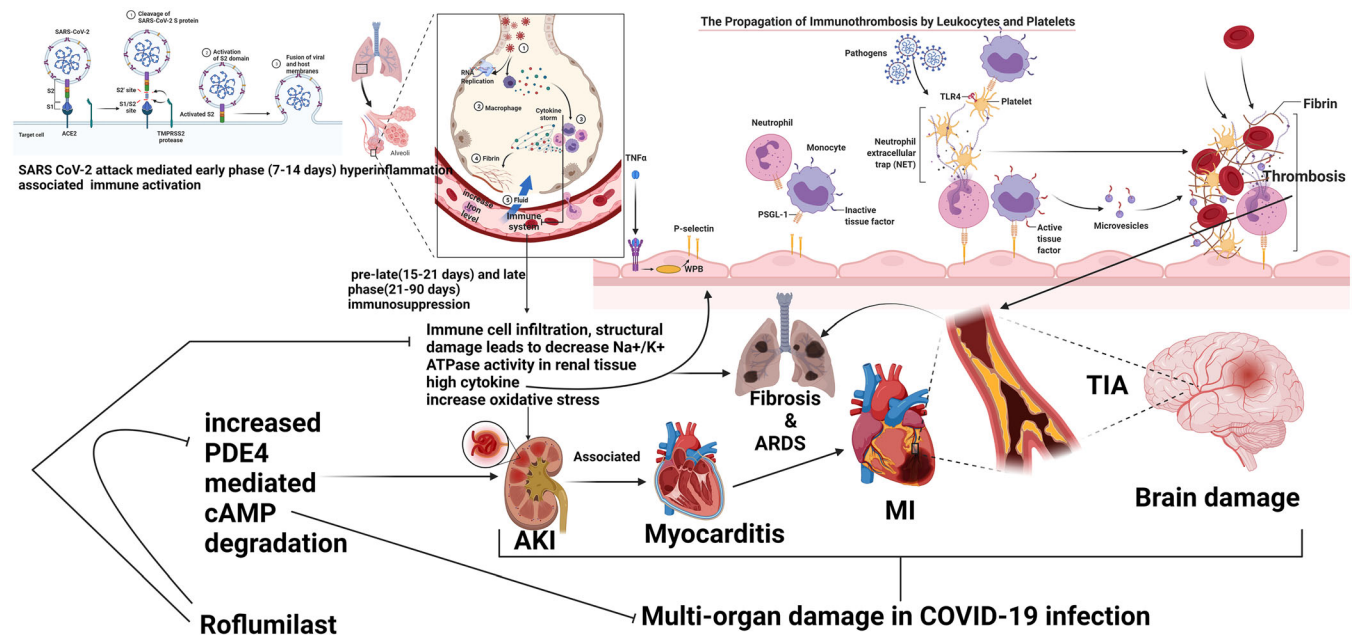
Proinflammatory cytokines including as interferon-gamma (IFN- $\gamma$ ), interleukin (I.L.)-1/2/6/8 and tumour necrosis factor (TNF)- $\alpha$ , which circulate early in the SARS CoV-2 assault, directly worsen the damage by recruiting diverse leukocyte populations to the site of injury, culminating in a severe inflammatory pathway. As a result of this overexcitation, immune cells, including natural and acquired host defence systems, become overloaded, releasing more proinflammatory cytokines that accumulate or are cleared from the glomerulus, causing damage to tubular nephron segments metabolic dysregulation mediated by epithelial cell death.<sup>2,3</sup> Furthermore, in laboratory experiments, leukocyte-platelet (P.L.T.) function has been proven to be integral to leukocyte recruitment<sup>4</sup> and the progression of the vascular inflammation and thrombosis.<sup>5</sup> Systemic inflammation is connected to a 'procoagulant' state in COVID-19 infection, characterized by overly increased tissue factor and factor VIIa levels. These findings imply that the prothrombotic activity of circulating leukocytes may contribute to the elevated cardiac, cerebral and renal vascular risk observed in individuals infected with COVID-19.<sup>6</sup> In the early stage of the SARS CoV-2 assault, hyperinflammatory and activation of the immune system, together with oxidation load lead to various pathological changes in renal tissue, including cell proliferation, podocyte (proteinuria), deposition of E.C.M. (extracellular matrix), pro-apoptotic factor activation. While the immunosuppression found in the late phase of COVID-19 disease/drug (steroids) associated impairs the body's defences, aggravating organ damage.<sup>7</sup> Furthermore, the peripheral blood count of monocytes and neutrophils in SARS CoV-2 patients implies immune system dysregulation at the late COVID 19 stage. In addition, the peripheral blood count in SARS CoV-2 patients for monocytes and neutrophils in this comparable time frame suggests immune system dysregulation at the late COVID 19 stage.<sup>8</sup> Additionally, aberrant blood neutrophil motility and an increased concentration of plasma leucocytes (CD10 and CD16, for example) both suggest an increased risk of death.<sup>8,9</sup>

Roflumilast was licensed for usage in the European Union in July 2010 as a PDE4 inhibitor. Roflumilast has been approved as a 'constraint' treatment to bronchodilators by the E.M.A. summary and, under the GOLD guidelines, an effect also exists in patients not controlled on the combination of Fixed-Dose LABAs like formoterol and I.C.S. such as beclomethasone dipropionate. Moreover, roflumilast coadministration with budesonide in Asians and Caucasians did not affect the steady disposition of either drug and had no consequences for its safety or tolerability, denoting that it may be consumed without or with a meal.<sup>10</sup> However, roflumilast cessation might be because of the relatively costly medicine and, after complex prescription

procedures or unpleasant effects, poor understanding of roflumilast indications between the clinicians.<sup>11</sup> A recent study found that roflumilast protects against the functional consequences of cerebral ischemia, which might be linked to its anti-inflammatory properties.<sup>12</sup> Another research also shows in particular that roflumilast inhibitor of PDE-4 prevents L.P.S. from releasing nitric oxide (NO), IL-1 $\beta$ , TNF- $\alpha$  from the production of the macrophage through suppression of activation of stress-activated protein kinases (SAPK)/c-Jun N-terminal kinases (J.N.K.), p38 mitogen-activated protein kinase (MAPK), nuclear factor-kappa B (NF- $\kappa$ B) mechanisms.<sup>13</sup> Roflumilast has been proven in animal preventative and curative studies to reduce bleomycin-induced lung fibrosis, lung hydroxyproline and right heart thickening; it has also been shown to prevent intracoronary pulmonary artery muscularization. The inhibitor PDE4 was utilized in the bronchoalveolar lavage fluid to diminish bleomycin-induced transcripts for TNF- $\alpha$ , transforming growth factor-beta (TGF- $\beta$ ), connective tissue growth factor synthesis, endothelin-1,  $\alpha$ (I)collagen and mucin Muc5ac in the lung, as well as to decrease the levels of IL-13, TNF- $\alpha$  and TGF- $\beta$ . Moreover, lung fibrosis,  $\alpha$ (I)collagen, right heart thickness generated by bleomycin have been reduced with roflumilast, but not dexamethasone group.<sup>14</sup> Additionally, another study found that roflumilast and roflumilast N-oxide suppressed the release of macrophages like cell attracting molecules and TNF- $\alpha$  release in the lungs.<sup>15</sup>

Inflammation and immunological response are strongly related to increased PDE-4 synthesis. There are five major PDE-4 isoforms. They are PDED-4A, PDED-4B, PDED-4C, PDED-4D and PDED-4E. PDE-4B is highly upregulated on neutrophils and monocytes, resulting in the discharge of many inflammation-inducing agents.<sup>16</sup> In contrast to earlier experimental findings, where L.P.S. injection was shown to stimulate TNF production from circulating leukocytes in PDE-4B knockout mice, it appears that this detrimental transcript effect in inflammatory conditions has been completely inhibited.<sup>17</sup> Additionally, suppression of PDE-4B repressed apoptotic cell death and inflammation molecule biosynthesis in the renal tubular epithelial cell when treated with cisplatin. Previously, when ovalbumin was given to rats' bronchiolar lavage fluid, PDE-4B/D expression was more significant than controls. The higher expression of these isoforms was noted in only the lavage fluid of rats with ovalbumin exposure.

However, the overexpression of PDE-4B only helped rescue allergic symptoms in this study.<sup>18</sup> The high-dose Roflumilast significantly reduced PDE-4B/D transcripts, suggesting key involvement of these two isoforms in ARDS linked with COVID-19. These data further indicate that inhibitions of both transcripts are adequate to raise cAMP levels in renal tissue that have a protective impact on the kidney. In addition, pre-treatment dosage of Roflumilast additively decreased renal oxidative stress, inflammatory cytokines and renal tissue M.P.O. expression. The M.P.O. neutrophil enzyme is strongly prooxidizing and proinflammatory.<sup>19</sup> Thus, roflumilast's anti-inflammatory and anti-oxidative actions in COVID-19 infection-induced acute renal damage might be attributable to neutrophil recruitment and migratory restriction.



**FIGURE 1** Depicts the possible role of roflumilast in SARS CoV-2 mediated inflammation to organ damage

Additionally, research indicates that roflumilast may be helpful in atherothrombotic disorders and inflammatory vasculitis that is not primarily associated with lung damage.<sup>20</sup> Notably, Roflumilast was found to improve glucose uptake and insulin sensitivity. This was linked with stimulation of the PKA/cAMP/CREB axis, which leads to PCG-1-dependent activation of mitochondrial energy production. Figure 1 Depicts the Possible Role of Roflumilast in SARS CoV-2 Mediated Inflammation to Organ Damage.

The current study reviewed existing data that the PDE-4 inhibitor protects renal tissues and other major organ systems after COVID-19 infection by decreasing immune cell infiltration. These immune-balancing effects of roflumilast were related to a decrease in oxidative and inflammatory burden, caspase-3 suppression and increased PKA/cAMP levels in renal and other organ tissue. The findings provide new information on the late-phase processes linked to COVID-19-related inflammation and the mechanisms behind roflumilast's organ-protective actions.

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#### COMPETING INTERESTS

The authors declare no competing interest.

#### AUTHOR CONTRIBUTIONS

Y.S., N.K.F. and S.F. proposed the study; V.S. and W.H.A. participated in all essential intellectual content sections of the study; F.A.A., I.K. and N.J. prepared figures; S.S.R. and G.G. proofread the whole manuscript. All authors approved the content of the manuscript.

#### DATA AVAILABILITY STATEMENT

No datasets were generated or analysed during the current study.

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