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.

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Letter to Editors

Inhaled milrinone for sick COVID-19 cohort: *A pathophysiology driven hypothesis!*

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Dear Editor,

COVID-19 has essentially emerged as a multi-systemic disease with endotheliitis at the heart of resultant organ dysfunction. The pulmonary endothelial cells substantially contribute to the progression of COVID-related acute respiratory distress syndrome (ARDS) associated with the breach of the vascular integrity accompanied by the inexorable widespread endothelial dysfunction leading to the pulmonary and systemic micro-circulatory alterations, perpetuation of the inflammatory cascade and cytokine release syndrome (CRS) and, the promotion of a procoagulant environment [1,2]. The recognition of vascular and coagulation pathophysiological networks of an ongoing endothelial disease in the sick COVID-19 cohort doubtlessly calls for a more endothelium-centric treatment approach.

Moreover, amidst the ardent discussions on the role of nitric oxide (NO) deficiency in accentuating the endothelial dysfunction in COVID-19, the whole NO and closely related downstream pathways have presented viable therapeutic opportunities to the fraternity [3]. In this context, phosphodiesterase enzyme (PDE) inhibition has captivated attention [4]. Within the purview of PDE inhibitors, we present a perspective on the therapeutic potential of inhaled Milrinone (iMil) in COVID-19, under the following heads:

A mechanistic-pathway of significance

While NO (endothelium derived relaxation factor) mediated vasodilatation is in itself intricately linked to an augmented cyclic monophosphates level in the vascular smooth muscle cells (v-SMCs), the contribution of PDE inhibition in preventing the enzymatic hydrolysis and subsequent termination of vasodilatory effects of cyclic adenosine and guanosine monophosphates (cAMP and cGMP) cannot be overlooked, particularly in a scenario of COVID-associated vasculopathy [3–5]. Herein, Mil classifies as a PDE3 inhibiting member of the PDE family and presents a rather familiar therapeutic option.

Wide biological target expression

Mil biological targets: PDE3A and 3B subtypes are widely expressed across the v-SMCs (cardiovascular system), airway SMCs, bronchial epithelial cells, fibroblasts, T-lymphocytes, megakaryocytes and macrophages. The cardiovascular and pulmonary expression profile of the drug endorse unique clinical promises pertinent to COVID-19 [4,5].

An exclusive therapeutic stance for iMil

An intravenous Mil infusion has been reported to assist a successful management of a spectrum of isolated COVID-19 adult and pediatric cases, for instance, in an adult setting of fulminant myocarditis and multisystem inflammatory syndrome in children (MIS-C) [6,7]. Despite the combination of inotropic and pulmonary artery dilatation (inodilator) and, lung endothelial function preservation properties of Mil being pivotal to the amelioration of pulmonary hypertension, deteriorating myocardial pump function and endotheliitis in COVID-19, the often associated enhanced vasopressor requirement owing to the systemic vasodilatory effects of intravenous Mil present peculiar management challenges [2,8,9].

Quite understandably, avoiding the untoward systemic effects, iMil can achieve the other drug benefits relevant to a COVID-19 setting. Nevertheless, the platelet counts should be closely monitored in patients receiving Mil through any of the administration routes. Furthermore, cAMP (potentiated by PDE inhibition) is a key secondary messenger in modulating the CRS through involvement in the protein kinase A and nuclear factor kB (NF-kB) inflammatory pathways. Enhanced intracellular cAMP levels shift the tenuously balanced inflammatory milieu in favour of the anti-inflammatory mediators such as interleukin-10 in addition to suppressing the major pro-inflammatory cytokines like tumour necrosis factor alpha (TNF-α) [4,5]. At the same time, an increased intracellular cAMP concentration reinforces the microvascular barrier, stimulates alveolar fluid clearance and inhibits neutrophil chemotaxis [10]. The description of a potential anti-remodelling, immunomodulatory and bronchodilator role of PDE inhibition also

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add to the contextual significance [5].

Encouraging literature

While Albert and colleagues demonstrate the safety and feasibility alongside a debatable efficacy of iMil administration in their small prospective study in adult ARDS patients [11], the Lamarche and colleagues description of a superior post-cardiopulmonary bypass (CPB) preservation of endothelial function heralded by a better postoperative hemodynamic and oxygenation profile of iMil compared to an intravenous infusion in a porcine model, merits elucidation [9]. Lamarche et al administered iMil bolus of 60–90 μg/Kg nebulised through the endotracheal tube over the 15 min preceding the CPB initiation followed by a maintenance iMil (a preparation of 200 μg/mL in normal saline, 2 mg drug diluted in 8 mg saline) employing a traditional in-line nebulizer (connected to the inspiratory ventilatory limb) at a continuous rate of 0.08–0.11 μg/Kg/minute throughout the CPB [9]. Their study findings stand particular relevance in consideration of the endothelial dysfunctional consequences of COVID-associated CRS which is in many ways related to the endotheliitis owing to a systemic inflammatory response to CPB [1,2,9].

Bueltmann and colleagues reveal an attenuated experimental acute lung injury with iMil in two separate animal models [10]. Their elaboration of a retarded elevation of wet-dry lung weight ratio, systemic hypoxemia and, bronchoalveolar lavage myeloperoxide activity, neutrophils and TNF-α levels in the animal groups receiving iMil, is certainly noteworthy [10]. Beute and colleagues also highlight the anti-inflammatory potential of iMil in house dust mite inflicted allergic airway inflammation in mice [12].

Conclusion

An improved comprehension of the COVID-19 pathobiophysiology should be closely backed by the meticulous investigation of the mechanistically related and specific drug therapies aimed at ameliorating the root cause of the disease process. Amidst the intensifying research challenges in the ongoing pandemic where a part of fraternity is impressing upon the fact that the plural of anecdotes does not classify as data [13,14], the importance of rapidly responding to the dynamic challenging clinical landscape cannot be overemphasized wherein a judicious application of more familiar medications such as iMil can be helpful in mitigating the ever growing concerns of COVID-19 attributable morbidity and mortality.

CRediT authorship contribution statement

Rohan Magoon: Conceptualization, Writing - original draft. **ItiShri:** Writing - review & editing. **Jasvinder Kaur Kohli:** Writing - review & editing. **Ramesh Kashav:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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