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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COVID-19 induced ARDS, and the use of galantamine to activate the cholinergic anti-inflammatory pathway

The current ongoing pandemic of SARS-CoV2 is a new challenge for the medical research community. Every avenue that can be tried should be tried in these desperate times. A lot of clinical research done in the area of COVID-19 induced ARDS , points to the direction that **immunomodulators** seem to have a protective role. Hydroxycholroquine [1], tocilizumab [2], and recently dexamethasone [3] has been shown to improve clinical outcomes in patients. This observation is probably due to the suppression of a **cytokine storm**, which has been implicated in the lethality of viral pneumonia [4].

I would like to bring into attention a novel pathway of immunomodulation, **The Cholinergic nervous system**. Early studies by Dr. Koopmans's lab had shown that **Vagus Nerve Stimulation** inhibits cytokine production and attenuates disease severity in rheumatoid arthritis [5]. They showed that an implantable vagus nerve-stimulating device in epilepsy patients inhibited peripheral blood production of TNF, IL-1β, and IL-6. Vagus nerve stimulation in Rheumatoid Arthiritis patients significantly inhibited TNF production . Moreover, the disease severity, as measured by standardized clinical composite scores, improved significantly. These were the earlier evidence of the parasympathetic nervous system having a role in modulating the immune system. The circuit came to dubbed as the "**cholinergic anti-inflammatory pathway**". It was found that this effect was mediated by **acetylcholine (ACh) stimulation of nicotinic receptors** on splenic macrophages. Subsequent work identified the **α7 nicotinic ACh receptor** (α7nAChR) as the crucial target for attenuation of pro-inflammatory cytokine release from macrophages and dendritic cells. Further investigation made the important discovery that **cholinergic T cells** within the spleen and not cholinergic nerve cells were the source of ACh that stimulated α7 receptors on splenic macrophages [6].

It can be theorized that there are two avenues to increase this cholinergic tone. First, by inducing the release of more acetylcholine as shown in Vagal stimulation, or second, by using an **acetyl-cholinesterase inhibitor.** Studies in rodent models have shown that increasing parasympathetic tone either using direct vagal stimulation, or acetyl cholinesterase inhibitors, increases the survival rate in animals with induced cytokine storms [7,10–13].

Galantamine is an alkaloid, first isolated from the bulbs of *Galanthus nivalis* (common snow drop) by Bulgarian chemist D. Paskov in 1956 [8]. It has been approved by the FDA to treat mild to moderate vascular dementia and Alzheimer's disease. Galantamine is a potent allosteric potentiating ligand of the **human nicotinic acetyl choline receptor** (nAChR), the same receptor, whose activation is implicated in the cholinergic anti-inflammatory pathway.It also acts as a competitive reversible inhibitor of acetyl-cholinesterase [9], further increasing its potential to increase the cholinergic tone.

Animal models of ARDS have shown to benefit from galantamine, in decreasing the mortality rate [10]. In one study on mice, Lipopolysaccharide induced Acute Lung Injury, the total mortality rate in control group was close to 80% vs 10% in the treatment group at 5 mg/kg [11]

I would suggest a hypothesis based on the above evidence that Galantamine can be a potential option of treatment for ARDS in COVID19 patients. Also given the extensive safety profile of the drug, and it's FDA approval, following gradual escalation protocols, expected cholinergic side-effects should be minimal.

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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