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Phosphodiesterase Type 5 Inhibitors and COVID-19: Are They Useful In Disease Management?

Nicola Mondaini

Urology Unit, Villa Donatello Hospital, Florence, Italy

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COVID-19 is an acronym formed by "CO" for "corona," "VI" for "virus," and "D" for disease. The "19" represents 2019, the year when the infection started [1]. Recently, Varga et al [1] showed the presence of viral elements within endothelial cells and an accumulation of inflammatory cells. These findings suggest that infection with SARS-CoV-2 (the virus that causes COVID-19) facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement (as noted based on the presence of viral bodies) and activation of the host inflammatory response. This progressive endothelial thromboinflammatory syndrome involves the microvascular bed of many vital organs, leading to multiple organ failure and death. This is the principle of interstitial pneumonitis that progresses to pulmonary failure [2]. Yang et al [3] recently published a small, but very informative systematic review and meta-analysis on the prevalence of comorbidities associated with COVID-19 infections in China, and they reported that diabetes was prevalent in 8% of cases, highlighting that this is somewhat in line with the prevalence of diabetes (10.9%) in Chinese adults. Diabetes in fact causes endothelial damage; for this reason, patients with diabetes who already have a damaged endothelium are probably more sensitive to the effects of COVID-19 [4].

Patients with diabetes often also have erectile dysfunction, which is nothing more than endothelial dysfunction, and in such patients, the use of phosphodiesterase-5 (PDE5) inhibitors is recommended to treat erectile dysfunction. Thus, like diabetes, the presence of erectile dysfunction could also represent a symptom to be taken into consideration when predicting the prognosis of patients with COVID-19. This possibility points to a potential role of PDE5 inhibitors in the management of COVID-19 [5]. The PDE5 inhibitor sildenafil citrate is a vasodilator that was approved in 1998 for treating erectile dysfunction and more recently received an indication for pulmonary arterial hypertension and idiopathic pulmonary fibrosis [6]. Sildenafil is currently under investigation in a phase 3 trial in patients with COVID-19 (NCT04304313), which will help clarify its therapeutic potential [5]. The goal of sildenafil treatment is to prevent or perhaps block the progression of fibrosis and to improve respiratory parameters in patients. Tadalafil has also shown

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Correspondence to: Nicola Mondaini https://orcid.org/0000-0002-5734-1725
Urology Unit, Villa Donatello Hospital, Via Attilio Ragionieri 101 Sesto Fiorentino, 50100 Firenze, Italy.
Tel: +39-347-3634734, **Fax:** +39-055-2396068, **E-mail:** info@nicolamondaini.it

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PDE5 inhibition with an IC_{50} of 5 nM. It possesses high selectivity for PDE5 *versus* PDE1–4 and PDE6. In particular, tadalafil is more selective against PDE5 than PDE6, whereas sildenafil shows similar potency to inhibit PDE5 and PDE6 [7]. Theoretically, the once-daily use of tadalafil, which is a long acting drug, could be useful to improve tissue vascularization and to combat fibrosis. Tadalafil is probably less effective in the acute phase, but could lend itself to use once daily for possible prevention in patients with erectile dysfunction who are not interested in sexual activity, and for similar purposes it could be administered to all discharged patients recovering from COVID-19.

For this reason, daily tadalafil could be a possible post-infection treatment, as its pharmacokinetic parameters, such as half-life and efficacy, make it an ideal candidate. No clear evidence exists regarding the possibility of SARS-CoV-2 infection in the testes, where sclerosis could result in fertility problems.

Therefore, my suggestion is to evaluate the use of daily tadalafil in future trials to block or prevent endothelial sclerosis in COVID-19 patients.

Conflict of Interest

The author has nothing to disclose.

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