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Old Wine in New Bottle: Concept of Drug-Repositioning in COVID-19

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Editorial

Since the first reports of a novel Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), emerged from the province of Wuhan, China in December 2019 [1], it has brought the entire worldwide to a standstill and impacted every single individual on the planet. In this age of globalization, as expected, the eyes of the world have been vehemently focused on the medical fraternity in hopes of a so far elusive cure. In spite of hundreds of clinical trials, anecdotal reports and off-label attempts, no therapy has proven to be effective in improving outcomes nor provide effective prophylaxis.

Intense social, political and media scrutiny, along with the sheer scale of the pandemic, have presented a unique challenge to the medical and scientific fraternity to be able to develop effective remedies in an extremely limited amount of time, and at times, with limited resources as well. Unfortunately, the discovery and licensing of a nascent molecule as an effective drug involves a prolonged gestational period, creating an unacceptable lag between therapeutic need and availability. Drug repurposing, a novel approach which involves identification of new indications for pre-existing drugs, is an economic and time saving endeavor [2], allowing a drug to directly enter phase III or IV clinical trials, thereby saving billions of dollars in production cost [3].

Much like the Middle East Respiratory Syndrome virus (MERS), the SARS-CoV-2 spreads through the respiratory route; however, unlike the former which utilizes Dipeptidyl Peptidase 4 (DPP4), it utilizes Angiotensin Converting Enzyme 2 (ACE 2) as a receptor to enter cells [4,5]. Fusion, is followed by endocytosis of the virion, which is facilitated by an acidic environment, wherein comes in to play diprotic bases such as hydroxychloroquine and chloroquine [6]. Activation of the main RNA Dependent RNA Polymerase (RDRP) enzyme requires proteolysis by a viral protease. Inhibition of the latter by anti-retroviral agents such as lopinavir, ritonavir and darunavir hold therapeutic promise [6]. Agents targeting RDRP such as remdesivir, favipiravir and arbidol have demonstrated some degree of *in vitro* and *in vivo* activity against SARS-CoV-2.

Numerous drugs previously in clinical use have been shown to act *via* amelioration of the cytokine response to SARS-CoV-2 infection. Tocilizumab, a monoclonal antibody, previously used for rheumatoid arthritis, acts by blocking the Interleukin receptor 6 (IL-6) [7]. Recent studies have promise of this agent in patients at risk of cytokine storms [8]. Ivermectin, a broad spectrum anti-parasitic agent, has shown *in vitro* activity against SARS-CoV-2, presumably through inhibition of nuclear viral transport [9]. Currently, dexamethasone, a corticosteroid with a plethora of uses, has been shown to reduce mortality in COVID-19 patients with Acute Respiratory Distress Syndromes (ARDS) [10]. An increased prevalence of thrombo-embolic complications in association with COVID-19 have brought into the foray anticoagulants [11,12].

Colchicine, a previously time-tested anti-inflammatory agent approved for rheumatological diseases such as gout and familial Mediterranean fever, has demonstrated promise in the treatment of COVID-19 [13]. Recently, antibiotics such as azithromycin and doxycycline have demonstrated promise in the treatment of SARS-CoV-2 through inhibition of viral replication and IL-6 production [14].

In conclusion, the concept of drug re-positioning has been vital in construction of a massive armamentarium of therapeutic agents against COVID-19. However, in view of lack of definite efficacy of most of these agents, large, well-designed, placebo control trials are desirable to establish management protocols.

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