

Re-purposive Use of Drugs in COVID-19: A Wake-up Call

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Due to unavailability of effective therapeutic agents and the anticipated time lag between the speed of spread of the novel corona virus (nCoV) (later re-named as severe acute respiratory syndrome-coronavirus-2, SARS-CoV-2) and the discovery of effective vaccines against corona virus disease-19 (COVID-19), various available anti-viral, anti-bacterial and anti-malarial drugs have been re-purposively used by physicians all over the world, with the hope to cut-down the huge human death-tolls and sufferings. Available evidences did not convincingly advocate their clinical use, though some favorable reports¹ exist amid the clinical context of COVID-19, but few of these evidences are retracted.

Ivermectin, a broad-spectrum endo/ecto-parasiticide has been shown to have a wide-spectrum anti-viral activity against many ribonucleic acid (RNA) viruses and few deoxyribonucleic acid (DNA) viruses, but the *in vivo* benefit of ivermectin was proven only against the West Nile virus and Newcastle disease virus.²⁻⁴ Ivermectin reduces serum concentrations of non-structural protein 1 (NS-1) in dengue but neither reduces viraemia nor has clinical benefit⁵, as is true for chikungunya and Zika. Because of the recent *in vitro* observation of ivermectin's inhibitory effect against replication of SARS-CoV-2 in first 48 hours and the *in vitro* and possible clinical utility of hydroxychloroquine and ivermectin, there arise the scope for clinical trials and then re-purposive use of ivermectin in COVID-19.⁶⁻⁹ Caution is sought by researchers regarding clinical use of ivermectin in COVID-19 and virtually, the concentration at which level *in vitro* anti-SARS-CoV-2 activity of ivermectin was discovered, is not attainable in conventional dosing regimens.¹⁰

News on electronic and print media^{11,12} in Bangladesh, describing the success of ivermectin and doxycycline combination in COVID-19, has made people very much enthusiastic of being treated by these drugs, in the absence of any acceptable remedy, till date. Availability of these low-cost drugs in medicine shops, in the absence of an effective monitoring system on medicine dispensing (without prescription), have made this

happen in Bangladesh. Reverse-transcriptase polymerase chain reaction (RT-PCR)-negativity within four days of starting therapy sounds miracle to general people, seemingly such to some practicing physicians and village doctors, who allegedly have started prescribing these combinations. But, the asymptomatic patients or those with mild symptoms do not merit any specific medication.¹³ As many patients were asymptomatic¹⁴, it was uncertain for how many days they were carrying the virus. So, such a correlation between the start of treatment and becoming RT-PCR-negative in asymptomatic patients remains a question of debate. If these patients could be compared with a similar cohort of COVID-19 patients on standard care or without any drug intervention, then it would sound a more logical claim; however, the authors have correctly recommended for further trials.

Another paper¹⁵ in this COVID-Supplement issue of the *Journal of Bangladesh College of Physicians and Surgeons* compared utility of ivermectin plus doxycycline and hydroxychloroquine plus azithromycin on viral clearance. In this study, outcomes of the two groups were evaluated in different time frames, on day 5 and day 11 respectively for the two aforementioned groups and that makes the comparisons disputed. The role of follow-up RT-PCR remains controversial; viral remnants in the respiratory tract may react positively and do not necessarily mean persistent infection, reinfection or infectivity.¹⁶ So, such reports require extreme caution during interpretation. Furthermore, the observations, that many severe and critically ill COVID-19 patients admitted in COVID-dedicated hospitals in Bangladesh had history of taking such medications at symptom onset, may raise question towards the beneficial effects of such drugs.

According to a published news¹², a clinical trial is on-way to compare the therapeutic effects of ivermectin, ivermectin plus doxycycline and placebo; the findings of this placebo-controlled trial including COVID-19 patients with different grades of severity and evaluating parameters like symptom relief, viral clearance,

requirement of oxygen and other supports, as well as drug adverse effects, are expected to be better evidences. Again, this trial is planned to recruit a small number of patients; findings from such a small study participants is likely to raise questions towards reliability.

Meanwhile, Bangladesh National Guidelines on Clinical Management of Coronavirus Disease-2019 reviewed its medication list.¹³ People are using many drugs without any definite proof of benefit. So, high-powered, randomized, double-blind, placebo-controlled trials recruiting larger numbers of COVID-19 patients with different severity groups, is expected to provide a reliable statement in this issue. Till then, it would remain as a wake-up call towards the treating physicians to remain very much cautious in re-purposive use of drugs against COVID-19 and “do no harm” to the patients.

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