LETTER TO THE EDITOR

MEDICAL REVERSALS AND CONTROVERSIAL DRUG THERAPIES DURING COVID-19 PANDEMIC

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To the Editor,

Medical reversal can be defined as a phenomenon when statistically more powerful results of new clinical trials lead to a change in clinical practice. While the list of the treatments performed during this pandemic is lengthy, we will be mainly focusing on Azithromycin, Anti-SARS-CoV-2 Monoclonal Antibodies, Chloroquine, Convalescent plasma, Hydroxychloroquine, Ivermectin, Remdesivir, Lopinavir and Ritonavir.

In February 2020, Wang M and *et al* suggested that Chloroquine can inhibit COVID-19 in vitro.[*et al*] However, a randomized control trial comparing low and high dose chloroquine was stopped early due to high mortality.[*et al*] One of the most widely publicized trials in favour of hydroxychloroquine reported that HCQ decreases the viral load despite the fact that just six patients received azithromycin with adjunctive HCQ and surprisingly no viral loads were recorded in these patients.[*et al*] Tang *et al* in an open-label trial found no difference in mild to moderate cases and two observational studies carried out in the United States also found no benefits.[*et al*]Concerns were also raised that these drugs put the patients at risk of prolonged QTc intervals. The RECOVERY trial investigators concluded that there was no benefit of using chloroquine and hydroxychloroquine for COVID-19 cases. And on June 15, 2020, the FDA (US) revoked the emergency use of these drugs stating that they should no longer be used outside the clinical trial setting. Similarly, WHO announced that they were stopping the hydroxychloroquine arm of the Solidarity trial. Therefore, unsurprisingly both chloroquine and hydroxychloroquine are no more recommended for the treatment of COVID-19. The proposed mechanism of action of convalescent plasma includes virus neutralization, antibody-dependent cellular cytotoxicity, and phagocytosis. In a small RCT carried out in Wuhan, some clinical improvement was observed in those patients who were not invasively ventilated.[*et al*]Despite the fact that most of the studies supporting the use of this intervention had limitations, in August 2020, the FDA authorized its usage for emergency use. However, in February 2021, this decision was reversed. They also argued that the use of the high titer plasma should only be considered during the initial stages of the disease and in those patients with impaired humoral immunity. In summary, the evidence was lacking as the results of the initial trials were inconclusive. And the landmark findings In the RECOVERY trial which was a RCT of convalescent plasma versus usual care, there was no significant differences in mortality.[*et al*] Presently, it is unclear which category of COVID-19 patients will benefit from the use of convalescent plasma therapy.

Gautret *et al* proposed that virological clearance is increased with the use of Azithromycin. But their study included just 36 patients and only six patients received the experimental drug and there was no control group.[*et al*]The largest randomized-controlled trial enrolling hospitalized patients with mild to moderate disease could not show any benefit from the azithromycin and hydroxychloroquine combination.[*et al*] Ray *et al* in their retrospective cohort study have shown that those patients who received a five-day course of Azithromycin were at higher risk of sudden cardiac death.[*et al*] FDA in June 2020, recommended against the use of Azithromycin in the treatment of Covid 19 patients. There is a lack of consensus about the use of Remdesisvir. FDA and NIH (USA) recommend the use of Remdesivir for hospitalized and ambulatory patients who are at risk of deterioration. On the other hand, WHO suggests that this anti-viral should only be used in the setting of a clinical trial. Adaptive COVID-19 Treatment Trial (ACTT-1) showed that treatment with remdesivir was associated with a reduction in recovery time when the treatment began early. Based on the preliminary results of this trial; the FDA issued an emergency-use authorization for remdesivir only 2 days after the initial press release. On the other hand, WHO SOLIDARITY trial which was a large open label trial involving 500 centers across 30 countries did not show any benefits in terms of hospital mortality or time to discharge.[*et al*] As a result of these findings, WHO Guideline Development Group (GDG) panel of international experts advised against the use of remdesivir in hospitalized patients, regardless of disease severity. Similarly, the results of the DISCOVERY trial did not show any difference in mortality and time to improvement in severe COVID cases.[*et al*] NICE guidelines recommend it for use in patients who are on low-flow oxygen with good liver and kidney function. Therefore, the overall evidence doesn't support the routine use of this antiviral in the management of COVID-19 infection but it can be considered in a trial setting.

Interest in Ivermectin began in early 2020 when Australian scientists found that it could stop viral replication in the laboratory. Surprising results were claimed by Elegazzar *et al* who found that it can result in 90% reduction in mortality. Their study was later retracted by the Research Square journal on 19[*et al*] July 2021. However, more decent quality trials later proved that there

is no benefit of Ivermectin in the prevention and treatment of COVID-19 infection.[et al] In April 2019, FDA approved emergency use authorization of Bamlanivimab and etesivimab for mild to moderate infection in non-hospitalized patients, and those who are likely to mount a poor response, and those with considerable risk of deterioration. Later in January 2022, FDA revoked its decision because these monoclonal antibodies are ineffective against the Omicron variant which according to CDC accounted for more than 99% of cases in the United States. Moreover, the expert panel also recommended against the use of REGEN-COV (cosirimivab and Imdevimab) because of markedly poor activity against the Omicron variant. On the other hand, the updated version (January 2022) of NICE guidelines recommends using Sotrovimab, or a combination of Casirivimab and Imdevimab in non-hospitalized patients and those who are at high risk of deterioration but the clinicians should keep in mind that the Omicron variant is resistant to these antibodies in vitro. In addition to this, NICE only recommends the use of a combination of Casirivimab and Imdevimab for adult hospitalized patients who do not have detectable antibodies in their blood.[et al]

Lopinavir is suggested for the management of COVID-19 due to its inhibitory action against protease enzymes. There is no doubt that Lopinavir has in vitro activity against this novel virus. But in a case series of eight COVID-19 patients that looked at its pharmacokinetic profile, only trough levels were studied, and it is unclear whether the virus can be effectively treated in humans with the plasma levels that were achieved which were many times lower than required to neutralize the virus.[et al] RECOVERY trial did not show any difference in 28-day mortality, the median time to discharge, probability of being discharged alive and risk of progression to intubation or death between the different groups. The study was statistically powerful resulting in the discontinuation of the Lopinavir/ritonavir arm by the experts.[et al]Similarly, the results of the Solidarity trial which was a randomized controlled trial did not show any benefit of Lopinavir/ritonavir in terms of mortality, length of hospital stay and initiation of mechanical ventilation. In summary, conflict of interest and unyielding confidence in basic sciences led to starting of a drug intervention which was later proved to be ineffective. The proponents of these therapies might argue that the drugs were introduced not to devoid anyone of the beneficial effect of drug treatment. But a reasonable approach would have been to start these therapies in a good quality trial where they should have been properly evaluated first, and then decisions made. This phenomenon is not new in practice. The case of Atenolol for hypertension and the coronary artery stenting in stable coronary artery disease are examples of medical reversals, and healthcare professionals can face similar challenges in the future.

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