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Letter to the Editor

2-Deoxy-D-glucose: is this the final cure for COVID-19: or yet another mirage?

Dear Editor,

The Government of India has recently introduced a promising new anti-COVID drug named 2-deoxy-D-glucose (2-DG). This drug was developed by the Institute of Nuclear Medicine and Allied Sciences, a laboratory of the Defence Research and Development Organisation (DRDO) in collaboration with Dr. Reddy's Laboratory, Hyderabad. At a time when India was struggling to survive the fatal second wave of the COVID pandemic, this drug was approved for emergency use as an adjunct therapy to moderate severe COVID patients claiming to cause speedy recovery and also reduced dependence on supplemental oxygen[1]. The sudden and rapid drug discovery process have raised doubts on the efficacy of this drug after the earlier disappointing results experienced with remdesivir and plasma therapy.

Following the initial pre-clinical studies conducted during April 2020 at DRDO and the Centre for Cellular and Molecular Biology (CCMB), Hyderabad, the Phase II clinical trials were performed across multiple sites on 110 patients admitted in 17 hospitals between May 2020 and October 2020[1]. However, it has been argued that the primary end point taken needed to improve on WHO's Clinical Progression Scale, and therefore, received criticism for not being an objective parameter[1]. Thereafter, Phase-III trials were conducted on 220 patients distributed in over 26 hospitals between December 2020 and March 2021, where it was observed that in both studies the method of blinding of clinicians was unclear[1].

Despite its hasty approval in India, 2-DG has no data available in the public domain or published on pre-print server (peer-reviewed publication in a journal takes longer) based on phase-3 clinical trials. Experts have also raised concerns regarding a few aspects of the clinical trials. For instance, the sample size of 220 subjects for phase-3 clinical trials were considered very small. Moreover, the logic and basis of calculating this sample size has not been explained. It is widely known that studies with such small sample sizes are usually not helpful in providing any conclusive information on the drug safety and efficacy[1].

The current therapeutic management of COVID-19 is mainly supportive; however, antiviral agents like remdesivir, lopinavir alone or in combination with interferon or ribavirin have displayed limited success in moderate to severe cases[2]. A variety of other treatment regimens like convalescent plasma and monoclonal antibodies have appeared to show potential at first but did not show much significant results. The search for "the anti-covid drug" still continues unabated worldwide.

2-DG is a glucose molecule which has the 2-hydroxyl group replaced by hydrogen, so that it cannot undergo further glycolysis. As such, it acts to competitively inhibit the production of glucose-6-phosphate from glucose at the phosphoglucoisomerase level which is an important step of glycolysis[3]. This drug has been previously used in the treatment of cancer cells by targeting the glycolytic pathway thus attributing to its radio and chemosensitising effects *in vitro* and *in vivo*, including its cancer preventive potential when taken as a dietary component[4]. It is true that this drug had been earlier suggested to be used as an adjuvant to radiotherapy in the treatment of COVID-19 pneumonia[5]. Further, it is an established fact that the metabolic reprogramming and enhanced glucose usage by aerobic glycolysis is the hallmark of cancer cells (Warburg effect)[6]. As observed in the clinical trials, a combination of

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radiation and orally administered 2-DG improved the quality of life with moderate survival benefit sparing the normal cells in cancer therapy[7]. The multiple mechanisms underlying this chemosensitisation has been elucidated and include depletion of energy, deranged redox balance, altered N-linked glycosylation leading to unfolded protein response, inhibited DNA repair, impaired cycle regulation, altered calcium influx and apotosis[8]. It has been previously reported that radiosensitisation of tumors with 2-DG administration is partly due to the immune stimulatory effects involving the restoration of CD4 to CD8 ratio and shift from Th2 to Th1, enhanced NK cells, improved antigen presentation (MHC II, CD80/86), and reduced Il-17[9]. In addition to this immunostimulatory effect, 2-DG in combination with radiation could generate anti-inflammatory response and mitigate bacterial infection[10]. Furthermore, it was observed that 2-DG alone could enhance the antigen presenting ability (MHCII and CD 86), functionality of macrophages and reduce TNFα, while increasing IFNγ[11]. Utilizing this potential of 2-DG was probably the primary intent of researchers when investigating new molecules for COVID-19 treatment.

Viral infection (both DNA and RNA viruses) causes a metabolic shift from oxidative phosphorylation to aerobic glycolysis in the host cell that favors viral replication[12]. The progression of COVID-19 disease linked with SARS-CoV-2 replication is also facilitated by enhanced aerobic glycolysis[13]. By causing impairment of glycolysis and preventing viral entry into the host cell, 2-DG appeared to be a promising candidate by demonstrating antiviral effects[14]. An *in vitro* study[15] had also shown that 2-DG could reduce the viral load in host cells as well. All these observations are strongly in favor of 2-DG. Nevertheless, the daily administration of 2-DG may warrant caution regarding its adverse effect on CNS and CVS[16]. There have been reports wherein at doses lower than the prescribed regimen grade 3 QT prolongation has been recorded[1].

The azido analog of 2-DG is also in the pipeline and is being proposed to have potential benefits in COVID-19 disease by quelling the cytokine storm. Meticulously planned preclinical studies in animal models comparing the efficacy and safety of 2-DG or its novel derivatives are needed prior to the designing of clinical protocols using this drug as a monotherapy or as an adjunct to the existing treatment guidelines.

This led to the suggestion that 2-DG be investigated for the therapeutic management of COVID-19, finally culminating in the fast approval by DCGI on 8th May 2021 for its use in moderate to severe cases of COVID-19.

Being readily available, cost-effective, and relatively easy to administer, 2-DG definitely holds promise for a developing country like India which has been vehemently battling the second wave of this pandemic with all its available resources. Since the approval of this drug is without the requisite large scale Phase III trials that normally involves a much larger sample size, it is difficult to predict whether the projected benefits shall be actually observed when used on a humongous population as India when it is commercially launched in June 2021. Moreover, the pharmacodynamic variations of this drug due to the heterogeneity in COVID-19 disease manifestations and inter-individual variations are yet to be visualized in a larger population.

Taken together, the nation stands with fingers crossed to witness the phenomenon which might prove this drug to be disappointing like remdesivir in reducing the mortality or morbidity of the disease or a great triumph over the disease at last. Only time will say.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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