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2-Deoxy-D-Glucose (2-DG) - The promising drug reduces oxygen dependence in hospitalized Covid-19 patients

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ABSTRACT

The emerging SARS-CoV-2 virus is an RNA virus that causes COVID-19 infection and corresponds to the Coronaviridae family. The newly sequenced virus appears to have originated in China and quickly spread all over the world, resulting in a pandemic that killed over 3,385,526 people until May 16th, 2021. As a result, researchers all over the world are working on an efficient vaccine to combat this disease, which will be critical in reducing morbidity and mortality. Covid-19 cases have been steadily increasing around the world due to a vaccine shortage. In collaboration with Dr Reddy's Laboratories (DRL), Hyderabad Institute of Nuclear Medicine and Allied Sciences (INMAS), a lab of Defence Research and Development Organisation (DRDO) has developed 2-deoxy-D-glucose (2-DG) for the emergency use, as additive therapy for moderate to severe COVID-19 patients. The drug was found to be safe and improved the recovery of COVID-19 patients significantly. By Day 3, a large number of patients had progressed symptomatically and were no longer dependent on supplemental oxygen, suggesting early relief from Oxygen therapy or dependency.

Keywords: SARS-CoV-2, morbidity, DRDO, INMAS, 2-DG.

INTRODUCTION

Viruses have the ability to do irreversible damage to humans. Coronavirus (Covs) was discovered to be the source of the common cold in 1960. Covs species can currently infect humans in seven different ways. Up to a third of community-acquired upper respiratory tract infections are caused by the four Covs species (HCoV-NL63, HCoV-229E, CoV-HKU1, and HCoV-OC43). SARS-CoV-1, discovered in 2002 as the cause of extreme acute respiratory syndrome (SARS), the Middle East respiratory syndrome, is one of the remaining three species that is highly pathogenic. In 2012, Covs was identified as the cause of the Middle East respiratory syndrome (MERS), and in 2019, SARS-CoV-2 was identified as the cause of Covs disease.(1) COVID-19 characterized by respiratory distress was first reported in December 2019, in the People's Republic of China. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic disease.(2)

Vaccination is one of the most efficient health initiatives in the world, preserving up to 3 million lives per year. Vaccination is the cheapest and most reliable way to control disease, so attempts are being made to develop COVID-19 vaccines in order to avoid a pandemic. Recombinant viral-

vectored vaccines, live attenuated viruses, protein subunit, inactivated vaccines, nucleic acid-based vaccines, and virus-like particles are examples of vaccine platforms.(3)Despite the development of multiple vaccines, due to a shortage, all human populations were unable to completely vaccinate. The second wave of the corona has begun to affect the citizens of small villages, and the number of cases is steadily rising, as is the death rate. The entire world is searching for an alternative medicine to minimize the number of people who need to be hospitalized. This article discusses the 2-DG medication, which aids in the quicker recovery of hospitalized patients and decreases the need for supplementary oxygen.

2DG

2-Deoxy-D-glucose is a glucose molecule with the 2-hydroxyl group substituted by hydrogen, preventing it from being glycolyzed further. As a result, it acts as a competitive inhibitor of glucose – 6 phosphate production from glucose at the phosphor gluco isomerase stage (step 2 of glycolysis). (4) Glucose hexokinase phosphorylates 2-deoxyglucose in most cells, trapping the substance. intracellularly 2-deoxyglucose-6-phosphate (with exception of liver and kidney) As a result, labelled types of 2-deoxyglucose are useful markers for tissue glucose absorption and hexokinase function.

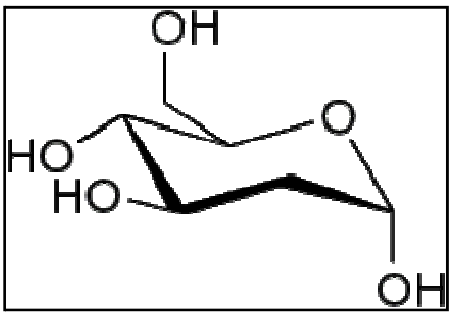

Fig 1: 2-Deoxy-d-glucose (5)

2-DG is taken up by the cell's glucose transporters. As a result, cells that take in more glucose, such as tumor cells, also take in more 2-DG. Since 2-DG inhibits cell growth, it has been proposed as a tumor treatment, and 2-DG is currently being tested in clinical trials. (6) The fact that 2-DG inhibits glycolysis does not seem to be enough to justify why 2-DG-treated cells stop developing. (7) Due to its structural similarity to mannose, 2DG has the ability to inhibit N-glycosylation in mammalian cells and other processes, resulting in ER stress and activation of the Unfolded Protein Response (UPR). (8 – 10)

Drug Controller General of India (DCGI) approved 2-deoxy-d-glucose (2-DG) for emergency use among people with moderate and severe COVID-19, to help manage the disease. This drug was jointly developed by researchers at the Institute of Nuclear Medicine and Allied Sciences, which falls under the Defence Research & Development Organisation (DRDO), and the pharmaceutical giant Dr Reddy's Laboratories. (11)

According to the INMAS-DRDO, the 2-DG, as a generic molecule and analogue of (similar to) glucose, can be easily produced and made widely available in the country. "Cheat the Cheater" is the basic operating concept. As we all know, once a virus enters the body, it makes its own copies by deceiving our human cells and stealing their protein in order to replicate. Any time a virus cell doubles in size, it needs glucose. So, the drug is merely a "Pseudo" Glucose that the multiplying virus consumes, but which ultimately renders it neuter. As a result of 'cheating the cheater,' once the virus's rapid replication is stopped, our own antibodies will easily combat it and defeat it within hours.

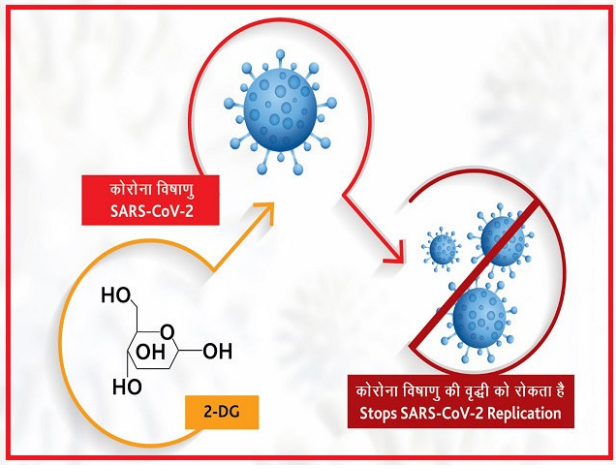

Fig 2: DRDO's anti-COVID drug 2-deoxy-D-glucose (2-DG) (12)

Dr Reddy's Labs had earlier said it believes that the proportionately high accumulation of 2-DG in the inflamed lung tissue of Covid-19 patients (as per PET scan study) due to the high metabolic activity induced by the coronavirus infection could lead to starvation in lung cells and result in inhibition of viral replication.

The drug has gone through the three phases of clinical trials. Published data for the trials is not yet available; however, as per the Ministry of Defence press release dated 8th May, 2021, "Clinical trial results have shown that this molecule helps in faster recovery of hospitalised patients and reduces supplemental oxygen dependence. Higher proportion of patients treated with 2-DG showed RT-PCR negative conversion in COVID patients."

"INMAS-DRDO researchers conducted experimental studies with the help of Centre for Cellular and Molecular Biology (CCMB), Hyderabad and observed that this molecule function efficiently against SARS-CoV-2 virus and impedes the viral growth. In Phase-II trials (including dose ranging) performed during May to October 2020, the medication was proven to be safe in COVID-19 patients and had shown marked improvement in their recuperation. Six hospitals participated in Phase IIa, and 11 hospitals participated in Phase IIb (dose ranging) clinical trials across the world. A 110-patient phase-II trial was performed. On different endpoints, patients treated with 2-DG showed quicker symptomatic cure than patients treated with Standard of Care (SoC). When compared to SoC, the median time to achieve normalisation of basic vital signs parameters showed a slightly favourable pattern (2.5 days difference).

Between December 2020 and March 2021, 220 patients were enrolled in the Phase-III clinical trial at 27 COVID hospitals in Delhi, Uttar Pradesh, West Bengal, Gujarat, Rajasthan, Maharashtra, Andhra Pradesh, Telangana, Karnataka, and Tamil Nadu. DCGI received detailed data from a phase-III clinical trial. In comparison to SoC, a slightly higher proportion of patients in the 2-DG arm improved symptomatically and were free of supplemental oxygen dependency by Day 3 (42 percent vs 31 percent), suggesting an early relief from Oxygen therapy/dependence. A similar pattern was found in patients over the age of 65."

The study conducted at the Centre for Cellular and Molecular Biology, Hyderabad showed that cell cultures in a laboratory without 2-DG had more viral plaques – clear spots indicating cell damage by the virus – compared to the ones with 2-DG. These experiments show that 2-DG can inhibit viral growth.

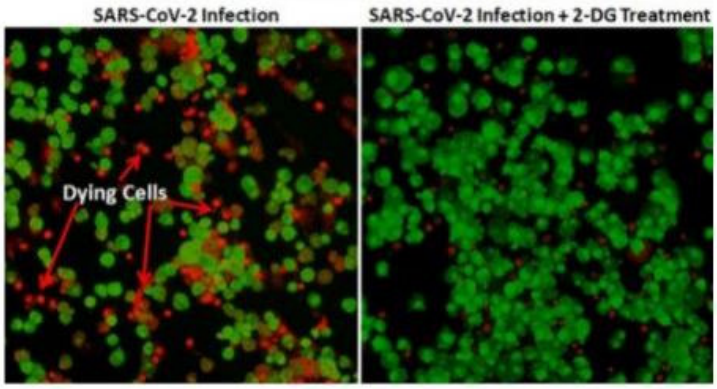

Fig 3: 2 DG inhibits SARS-CoV-2 growth (12)

The Drug Controller General of India (DCGI) has approved the emergency use of 2-DG as additive therapy for moderate to severe COVID-19 patients**.** Being a generic molecule and analogue of glucose, it can be easily produced and made available in India. The anti-COVID-19 drug has been developed by the Institute of Nuclear Medicine and Allied Sciences (INMAS), a lab of Defence Research and Development Organisation (DRDO), in collaboration with Dr Reddy's Laboratories (DRL), Hyderabad. (12)

2-deoxy D-Glucose (2-DG) comes in Sachet 5.85 g and 2.34 g. Sachet contains white color granular powder. These granules are filled in Laminate made of Glassine Paper / LDPE (Low Density Polyethylene) / Aluminium Foil / LDPE. It should be store at 25°C (77° F). Excursions are allowed between 15-30°C (59-86°F). It has to be taken orally by dissolving it in water for 5-7 days. The drug accumulates in the virus-infected cells and prevents its growth by stopping viral synthesis and energy production. The USP of the drug is its selective accumulation in virally infected cells. In the ongoing second wave of the COVID-19 pandemic, patients are facing severe oxygen dependency and need hospitalisation**.** In such a scenario, the anti-COVID drug is expected to save lives due to the mechanism of operation of the drug in infected cells**,** thereby reducing hospital stay of the COVID-19 infected patients. (11)

2GD's mechanism of action is as follows: This drug's selective accumulation in virally infected cells is one of its distinguishing features. It stops viral synthesis and energy production as it accumulates in virus-infected cells, preventing virus growth (multiplication). 2-DG has already been investigated as a cancer treatment. "The ability of 2-deoxy-d-glucose (2-DG) to disrupt d-glucose metabolism shows that nutrient and energy depletion is an effective method for inhibiting cancer cell growth and survival. 2-DG, which acts as a d-glucose mimic, inhibits glycolysis by forming and accumulating 2-deoxy-d-glucose-6-phosphate

(2-DG6P) within cells, inhibiting hexokinase and glucose-6-phosphate isomerase, and causing cell death." (13)

CONCLUSION

The clinical trials established that a higher proportion of those administered with the DRDO-developed drug "improved symptomatically" by the third day of their treatment, as compared to those provided the standard treatment. The first batch of 10,000 doses of 2DG medicine for the treatment of COVID-19 infected patients was launched on 17th May 2021 & given to patients**.** As a result of the current second pandemic wave, there is a high demand for oxygen, and this treatment has arrived at the right time. Hospitalization can be reduced by lowering oxygen demand. The price of this drug has yet to be decided, but we hope that it will be available to the vast majority of people, and thus help save precious lives.

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