Review Article

Role of 2-Deoxy-D-Glucose (2-DG) in COVID-19 disease: A potential game-changer

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Abstract

Virus infections can cause tissue damage in many ways. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a cause of the current COVID-19 pandemic, has been extensively studied so far to investigate its pathophysiology and evaluate its impact on the metabolic system of human cells. This has given a lead to study the role of 2-deoxy-D-glucose (2DG) against COVID-19 disease. We hereby would like to briefly discuss the concept and rationale behind the use of 2DG COVID-19.

Keywords: COVID-19, glucose, 2-DG

Introduction

Currently, COVID-19 patients are treated based on the disease severity. In India, moderate to severe category patients are treated with oxygen support and intravenous steroids. Drugs like remdesivir and tocilizumab are only suggested to be used in selected patients [All India Institute of Medical Sciences (AIIMS) protocol dated 17 May 2021]. Various other drugs have been tried across the globe with different outcomes. On similar lines, 2-deoxy-D-glucose (2DG) has been approved by the Indian Council of Medical Research (ICMR) on 1st May 2021. During the 1st wave, India was able to successfully contain the spread and death toll to a significantly low level.[1] This drug has come at a time when India is going through the 2nd wave of the COVID-19 pandemic with worrisome morbidity and mortality figures. As of 21st May 2021, India is reporting almost 300,000 to 350,000 new COVID-19 cases on daily basis with close to 1000 deaths per day. Hence, scientists, physicians, and patients are looking forward to this new potential drug that might change the trajectory of the COVID-19 pandemic in India.

What Do We Know So Far About 2DG?

Diagnostic role

2-DG is essentially a glucose molecule in which, the 2-hydroxyl group gets replaced by hydrogen. Due to this chemical replacement, 2DG is not able to enter glycolysis and contribute to ATP production. DG otherwise can be attached to various radioactive substrates and currently is being extensively used in various diagnostic tests and laboratory studies. For instance, in a positron emission tomography (PET) scan study, 2-DG is commonly used as a chemical dye. When a PET study is done in a patient with suspected cancer, 2-DG is preferentially taken up by tumor cells in an excessive amount due to the high metabolic rate. The radiolabeled 2-DG allows these cancer cells to glow prominently to be picked up in imaging.

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Anticancer role

The Warburg effect is one of the well-studied concepts in cancer biology which suggests a cause-effect relationship between cancer development and the increased aerobic glycolysis within the cells.[2] 2DG is considered to interrupt the glycolysis and hence block the subsequent growth of cancer cells [Figure 1].[3,4] In addition to this, 2-DG reduces glycosylation and inhibits the pentose phosphate pathway which indeed inhibits angiogenesis, and increases autophagy and apoptosis of cancer cells.[5]

Antiviral role

There is already enough literature and studies on the potential role of 2DG for its antiviral activity.[6,7] *In vitro* studies on the herpes virus have shown that 2-DG affects the early stages of the viral replication cycle including reduced cell penetration by the herpes virus in presence of 2-DG.

2-DG in COVID-19

Although the vaccine is available now, and there is a mass campaign going on in India and other countries to vaccinate as many people as possible in the shortest time. However, vaccination with two doses with a duration of at least 3–4 weeks and a huge population are a few of the major hurdles ahead which demand to still aggressively find alternative, effective, and safe drugs to treat symptomatic patients with COVID-19. Remdesivir, tocilizumab, plasma therapy, and many other investigational drugs have been tested and are currently being used against COVID-19 with variable outcomes.[8,9] 2-DG can be considered as another attempt by scientists to fight against this deadly virus.

Interestingly, a recent *in vitro* study by Codo *v.* showed that increased glucose levels and glycolysis promote SARS-CoV-2 infection.[10] They also noted that to have an upregulation of many glycolysis-associated genes in bronchoalveolar lavage (BAL) monocytes of COVID-19 patients. With these findings, Condo *et al.* proposed that at least in monocyte cells, increased glycolysis is specific to SARS-CoV-2 and could be considered as a potential pathway to target.

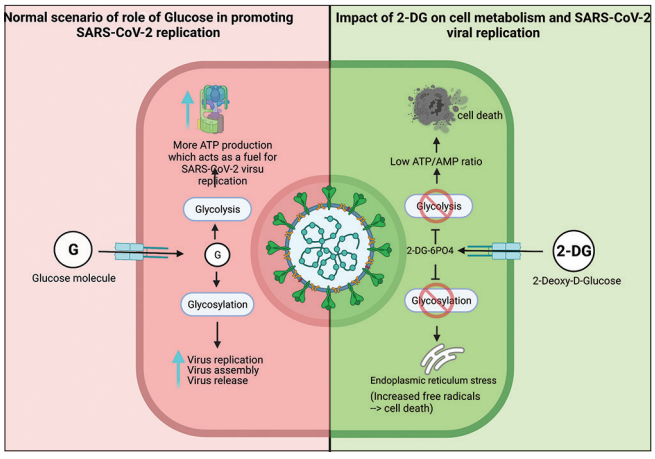

Figure 1: Impact of glucose versus 2-DG on cell metabolism and SARS-CoV-2 viral replication

Indian Study on 2-DG in COVID-19

Institute of Nuclear Medicine and Allied Sciences (INMAS)- Defense Research and Development Organization (DRDO)-Dr. Reddy's Laboratories Collaboration

A recent study on 2-DG in COVID-19 patients was conducted by the Institute of Nuclear Medicine and Allied Sciences (INMAS), a lab of Defense Research and Development Organization (DRDO), in collaboration with Dr Reddy's Laboratories (DRL), Hyderabad, India.[11] INMAS-DRDO scientists initiated Phase II clinical trial on 2-DG in COVID-19 patients approximately a year ago in May 2020 during the 1st wave of the pandemic [Figure 2]. This was followed by a Phase III study and a recent approval on May 01, 2021, by Drugs Controller General India (DCGI) for emergency use of 2-DG as an adjunct therapy in patients with moderate to severe COVID-19.[12] As per the interim available data, the Phase-II trial reported a median time difference of 2.5 days to achieve normalization of specific vital signs parameters in the 2-DG arm when compared to Standard of Care (SoC). Subsequently, the Phase III trial was pursued which showed that a higher proportion of patients improved symptomatically and became free from supplemental oxygen dependence in the 2-DG arm (42%) when compared to the SoC arm (31%) by the end of day 3 of treatment [Table 1].

Other authors have proposed a combination therapy of using adjuvant 2-deoxy-D-glucose with low-dose radiation therapy against COVID-19 pneumonia.[13] Other similar molecules like 2-azido-2-DG, 2-fluoro-deoxy-glucose, and WP112 (prodrug for 2-DG) have been studied previously for their capability to produce oxidative stress preferentially inside the virally infected cells that ultimately leads to cell death.[5,14] These molecules can also be candidates to conduct similar research.

Potential Side Effects of the Use of 2-DG in COVID-19

It is too early for us to comment on the side effects of the use of 2DG in patients with COVID-19. But as with any drug, 2-DG is also not side effect free based on the previous studies conducted on cancer.[15] These studies have found that 2-DG when used up to 63 mg/kg is a clinically tolerable dose. Beyond this dose, various potential side effects of 2 -DG are reversible hyperglycemia, gastrointestinal bleeding, and QTc prolongation.[15] Amongst these side effects, probably QTc prolongation is of the most important as while managing COVID-19 disease, many physicians frequently use other arrhythmogenic drugs like macrolides and hydroxychloroquine.[16] Hyperglycemia could also worsen, especially when most of the

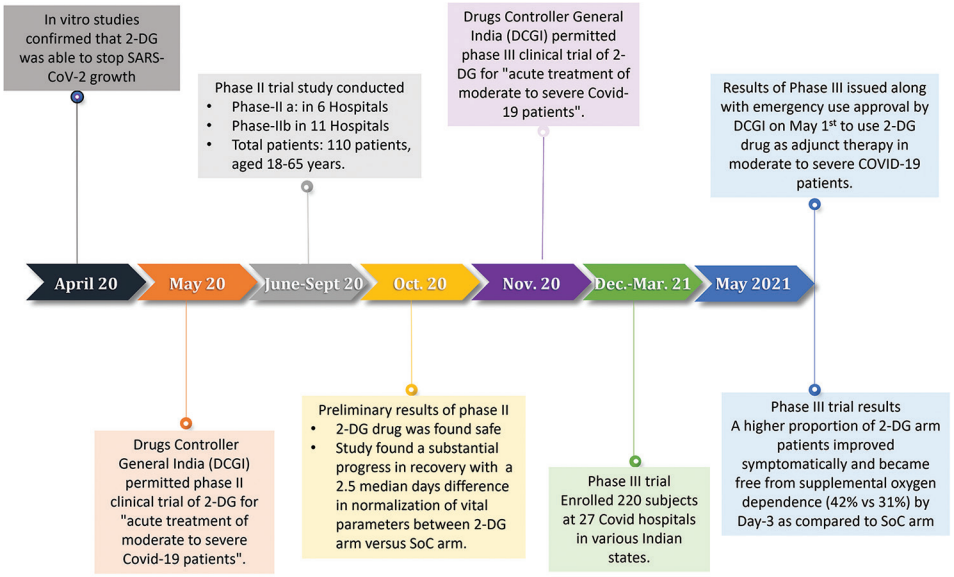

Figure 2: Timeline of the 2-DG drug trial conducted by INMAS-DRDO-Dr. Reddy's laboratories collaboration

moderate and severe COVID-19 patients are also on high doses of steroids.[17] As we move forward, capturing the data from patients on 2-DG would help us know more about the side effect profile of 2-DG.

Limitation of the INMAS-DRDO-Dr. Reddy's Study

The study conducted had several shortcomings that should be considered while inferring the conclusion. First, it had a small sample size with just 110 patients enrolled in the Phase II trial and 220 patients in the Phase III trial. Also, extremely ill patients with multi-organ failure, acute respiratory distress syndrome (ARDS), and those who were mechanically ventilated were excluded from the study. Also, patients with any form of chronic comorbidity were also excluded from the study. This exclusion criteria technically sorts out the most "high-risk candidates" who otherwise have a poor prognosis in general. We know that hypertension, obesity, patients with cancer, and transplantation are the ones who probably are the worst performers when acquiring COVID-19, and hence excluding this high-risk population from the study would deprive them of getting this potential anti-COVID 19 medication.[18-20] Though there is enough data on the safety and good tolerability of 2-DG in humans, most of the available literature on 2-DG is *in vitro* and lacks extensive human trials so far, so a concrete inference is difficult to extrapolate from this study. Lastly, the details of side effects were not shared so far, and hence we need to wait more before we can comment on this aspect of pharmacokinetics. The dose of 2-DG used in this study (90 mg/kg/day) is comparatively higher than the dose studied (63 mg/kg/day) previously in other cancer-related trials.[15] Hence, the likely chance of side effects could be detrimental due to the higher doses used in this study. Hence, it is important to know the side effects suffered by the patients in this trial.

Despite being extensively studied in the oncology field for almost 2–3 decades at least, 2-DG is still not approved for even cancer therapy. Similarly, with regards to COVID-19, the path of 2-DG ahead has a lot of potential obstacles which might be concerning to the scientific bodies thereby hampering its universal acceptance.

Future of 2-DG in COVID-19

As discussed above, 2-DG is a simple molecule and comparatively easy to develop, cost-effective measure as it is a glucose analog and hence potentially the production can be achieved on a larger scale. The approximate price of one sachet of 2-DG as per Dr. Reddy's laboratory is 990 rupees. There seems to be no concern for decay in shelf life as it is available in sachet/powder form and can be stored at room temperature (recommended to be stored under 25°C), so can be shipped easily from one part of the world to other. However, the results are preliminary and do require a good follow-up of the patients who will be receiving 2-DG. The development of an online data registry to capture the efficacy and side effects of 2-DG would be of extreme benefit to consolidating data of 2-DG use in COVID-19 disease.

Conclusion

We applaud the efforts of scientists from India in developing 2 DG as a potential anti-COVID-19 drug. The use of 2DG may emerge as a potential adjunct therapy that is cheap, easily available, and has a tolerable side effect profile. The relevance of ongoing study by Indian scientists becomes more important due to the very fact that this is the only active study currently on the "role of 2-DG in COVID-19." Although this is certainly a promising drug, it needs more confirmation of the preliminary data by conducting a

Table 1: Study details the 2-DG drug trial conducted by DRDO (India)

Parameters	Details of the Indian Study on 2-DG in COVID-19: INMAS-DRDO-Dr. Reddy's laboratories collaboration	
CTRI Number	CTRI/2021/01/030231	
Type of Trial	Interventional	
Type of Study	Drug Trail	
Study Design	Randomized, Parallel-Group, Multiple Arm Trial	
Scientific Title of Study	A Randomized, Open-Label 2-Treatment Group Clinical Trial Evaluating the Efficacy and Safety of 2-Deoxy-D-Glucose as adjunctive therapy to standard of care, in comparison to standard of care alone, in the Acute Treatment of moderate to severe COVID-19 patients	
Primary Sponsor	Institute of Nuclear Medicine and Allied Sciences INMAS (DRDO, Ministry of Defense)	
Secondary Sponsor	Dr. Reddy's Laboratories Limited	
Comparison between	Intervention	2-Deoxy-D-Glucose 45 mg/kg body weight AM plus 45 mg/kg body weight PM PLUS Standard of Care for 10 days or until discharge, whichever earlier.
	Standard of care only	For 10 days or until discharge
Primary Outcome	1. To evaluate the efficacy of 2-Deoxy-D-Glucose (2-DG) as adjunctive therapy to standard of care (SoC), in comparison to SoC alone, in the acute treatment of moderate to severe COVID-19 patients 2. To evaluate the safety of 2-DG as adjunctive therapy to standard of care (SoC), in comparison to SoC alone, in the acute treatment of moderate to severe COVID-19 patients	
Target Sample Size	220 patients	
Phase of Trial	Phase 2 followed by 3	
Inclusion Criteria	To meet all the criteria to be considered for the study: Any patient aged ≥18 years testing. Tested positive for SARS-CoV-2 by real-time reverse-transcriptase-polymerase chain reaction (rRT-PCR) on a nasopharyngeal or oropharyngeal swab and having moderate or severe COVID-19 disease severity	
Exclusion Criteria	Patients will be excluded in case of any of the following. 1. Critically ill patients (invasive mechanical ventilation and those with ARDS, septic shock, or multi-organ failure at baseline) 2. Beyond 10 days of COVID-19 illness was observed >10 days 3. Hypersensitivity or a contraindication to the IMP 2-deoxy-D-glucose or luorodeoxyglucose 4. Patients with a history of one or more known comorbidities 5. Patients who currently are or are expected to receive drugs potential of prolonging the QT interval of the heart including hydroxychloroquine or azithromycin. 6. Patients who received Interferon alpha or experimental biological therapies within 3 months. 7. Patients receiving other investigational therapies for COVID-19. 8. Patients with malabsorption or gastrointestinal abnormalities that may affect drug absorption. 9. Patients with body Weight <45 kg or >130 kg 11. Female patients who are pregnant or lactating 12. Recipients of organ transplantation within last 6 months or currently on immunosuppressive therapy 13. Patients who are contemplating surgery/female patients contemplating pregnancy within 3 months after the scheduled end of study treatment	
The outcome of Phase 2 trials	2-DG arm showed faster symptomatic cure than Standard of Care (SoC) arm on various endpoints (vital parameters) with a significantly favorable trend (2.5 days difference)	
The outcome of Phase 2 trials	1.In the 2-DG arm, 42% of the patients improved symptomatically and became free from supplemental oxygen by Day-3 in comparison to 31% in the SoC arm, indicating an early relief from oxygen therapy/dependence. 2. A higher proportion of patients treated with 2-DG showed RT-PCR negative conversion in COVID patients.	

Adapted from https://pib.gov.in/PressReleasePage.aspx?PRID=1717007 and http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=50985&EncHid=&userName=2-DG

multicentric study with a larger population and from different geographical regions.

Ethical statement

The article does not contain the participation of any human being and animal.

Verification

All authors contributed to data analysis, drafting, or revising the article have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

IRB approval

Not applicable

Consent

Informed consent was obtained from the patient to publish the case details and accompanying images.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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