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2-deoxy-D-glucose as India's Response to COVID-19: A Commitment or Conceit?

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Abstract

2-deoxy-D-glucose (2-DG) has recently been approved for the treatment of moderate to severe COVID-19 patients in India. Here we discuss whether this is a well thought-out step towards the long-term management of COVID-19 or a decision taken at the spur of the moment. 2-DG, an anticancer drug, also has immunomodulatory functions. Several studies have shown 2-DG to inhibit viral replication and cytokine storm. However, these findings are mostly on cells and animal models. The clinical trial that has become the basis of the approval of this drug in India is yet to be peer-reviewed and has not explicitly addressed several concerns, nor has it established its claim of faster efficacy with rigorous statistics and safety profile. Even though 2-DG shows much promise in COVID-19 treatment, its approval seems rather premature, which may prove to be more harmful than beneficial in the long run.

Keywords: 2-deoxy-D-glucose, Covid-19

Since the advent of the current pandemic, researchers worldwide have left no stone unturned to discover effective therapeutic agents to combat it. At times, they took the help of the technique of "re-purposing" of "time-tested" therapeutic agents that might have a role in barring the SARS-CoV-2 infection. Unfortunately, no such single "re-purposed" agent has been widely accepted to be effective against the disease until date.[1–4] Even with the emergence of multiple effective vaccines, the entreaty of effective drug treatment has eluded us. This might be due to inadequate availability, questionable efficacy and, at times, contentious safety profile of vaccines, and finally, yet importantly, the socioeconomic crises and sociopolitical frailty countries like India are going through.

The latest addition to this ever-enlarging armament of "COVID-19 therapeutics" has been the adjuvant anti-cancer drug, 2-deoxy-D-glucose (2DG),[5] claimed solely by Indian scientists.[6] On May 01, 2021, the Drugs Controller General of India (DCGI) granted permission for emergency use of the "glucose decoy" 2DG (developed by Institute of Nuclear Medicine and Allied Sciences, a lab of Defense Research and Development Organisation, in collaboration with Dr Reddy's Laboratories), as adjunct therapy in moderate to severe COVID-19 patients. A phase II trial permitted by the DCGI, and conducted between December 2020 and March 2021 on 220 patients encompassing several Indian states, claimed that patients who received 2DG had symptomatic improvement and were free from supplemental oxygen dependence by day 3 of treatment.[7] A higher proportion of patients treated with 2DG also showed RT-PCR negative conversion.[7] An in-silico preprint had previously claimed that 2DG, acting here as a protease inhibitor, gets efficiently tagged with SARS-CoV-2 receptors 3CLpro and NSP15 endoribonuclease, leading to the inactivation of receptors and incapacitation of the virus, ultimately resulting in both reduced viral entry and viral replication inside host cells.[8] However, a closer look at the trial protocol raises

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several concerns.[8] Specifically, the study recruited patients with moderate disease and without comorbidities (diabetes, chronic kidney disease, coronary artery disease, chronic obstructive pulmonary disease) or those receiving tocilizumab. In addition, the treatment claimed faster efficacy trends, but it was unclear how many of them received corticosteroids and no numbers were provided regarding statistical significance. The claimed result of patients improving from the drug required more validation regarding their survival, hospital stay, and proportion of patients going into mechanical ventilation. These pivotal questions lack answers. Furthermore, it is unclear how many patients had hypoglycemia, which is a major side effect.[9] With the small sample size, it was not easy to assess the safety profile of the drug.[9] Just as 2DG restricts cancer growth by acting on cancer cells heavily dependent on glucose, similarly, normal glucose-utilizing cells like neurons could be affected. Again, available clinical trial results point towards cardiac side effects (at a dose of 63 mg/kg/day), and thus, its safety profile is still questionable.[9] Last but not least, one wonders that with a trial where the phase II and phase III data have not been published, even as a preprint, and hence, have not undergone peer review of any sort, whether it is too early or even appropriate to approve a treatment on a mass scale. When India's response to COVID-19 has already faced much criticism,[10] inadvertent introduction of this metabolic re-programmer 2DG as a "decoy" might add to the prevailing setbacks.

A thorough scrutiny of the medical literature reveals that the usage of 2DG as an antiviral drug became popular during the seventies and eighties of the last century.[11–13] More recent studies have shown that besides metabolic reprogramming and anti-tumor activities, 2DG also participates in immunomodulatory activities such as enhancing phagocytosis (macrophage-functionalities), activity of MHC-II and CD86 (antigen-presenting cells activities), interferon-gamma, and blunts the release of tumor necrosis factor-alpha.[14,15] Varanasi et al.[16] reported that 2DG therapy mitigated pro-inflammatory effector T cells, but had no direct effect on regulatory T cells that play a protective function in herpes simplex virus-induced stromal keratitis lesions. Codo et al.[17] concluded that for survival and replication of SARS-CoV-2 inside host cells, glycolytic flux is sine-qua-non. They also demonstrated that 2DG mitigates both viral replication and cytokine storm through the inhibition of glycolytic enzymes (6-phospho-fructo-2-kinase/fructose-2,6-bisphosphatase-3), a positive regulator of phosphofructokinase-1, besides lactate dehydrogenase A and inhibition or stabilization of hypoxia-inducible factor 1-alpha.[17] Indeed, it inhibits SARS-CoV-2 replication in colon cancer cells.[18] Hence, 2DG might play an instrumental role in cellular energy metabolism by inhibition of glycolysis, leading to the downregulation of cytokine response and viral survival in the host.[19] As an adjuvant, it increases the effectiveness of low-dose radiation therapy in the treatment of COVID-19 pneumonia, especially in patients having cytokine storm.[20] Furthermore, Bojkova et al.[18] suggested the adjuvant role of 2DG to benfo-oxythiamine (a prodrug of oxythiamine, an inhibitor of transketolase, the key regulatory enzyme of the pentose phosphate pathway) in curtailing the supply of necessary ribonucleotides (generated by pentose phosphate pathway) to SARS-CoV-2, and thereby halting replication. Despite all the evidence, however, its value in the clinical setting is yet to be under thorough scrutiny, which begs the question of the decision to approve the drug on a mass scale in India.

Both clinically and pathogenetically, the drug offers promise for the treatment of SARS-CoV-2 infection (Table 1). However, history might not look back at us kindly if we, currently in the era of evidence-based medicine, make policy decisions not based on concrete evidence. We must collectively ensure that in these trying times, we raise the bar of scientific research, and we deliver our response and promises based strictly on science and our critical reasoning abilities, despite the lure of economic, political, and emotional challenges.[21,22] Back in the day, Kern et al.[23] failed to demonstrate any significant beneficial effects of 2DG in the four models of mucocutaneous infection with herpes simplex virus. Similar experiences were shared by other groups.[24,25] Finally, other than corticosteroids, the three most lucrative candidates for "repurposed" therapy are remdesivir (antiviral), tocilizumab (Il-6 inhibitor), and convalescent plasma-initially thought to have significant effects, and full commitment has now been found to be not so much.[1–3]

2DG is not yet extensively studied in COVID-19. No published efficacy or safety data are available and it could not be used in COVID-19 patients with comorbidities. Although its antiviral properties have been known since long, no international trials are heard to be ongoing or published at present. Moreover, approval for use as an antiviral (or even an anticancer agent for that matter) for treating any viral infection has not yet been given by any national and international authorities, perhaps due to doubts in efficacy, potential adverse effects, and the lack of any large-scale trials. Hence, whether it will come out as a commitment as initially promised or ends up, as another precipitous decision of conceit, remains to be a test of time.

Table 1. Potential merits and demerits of 2-deoxy-D-glucose.

Merits	Demerits
1. Being a generic molecule and analogue of glucose, it can be easily produced and made available in plenty in the country.	1. Unpublished data with no peer review.
2. The drug comes in powder form in a sachet, which is taken orally by dissolving it in water. It accumulates in the virus-infected cells and prevents virus growth by stopping viral synthesis and energy production. Its selective accumulation in virally infected cells makes this drug unique.	2. Difficult to administer with doses to be given after overnight fasting and a 3-h fasting, respectively.
3. There is data supporting the safety and tolerability of the drug, including in patients more than 65 years of age.	3. Only one study with small sample size for properly judging efficacy and safety profile.
4. It reduces the hospital stay of COVID-19 patients.	4. Suitable for those with moderate disease and without any comorbidities such as cardiac disease, diabetes, obesity, malnutrition, which practically excludes majority of the critical patients.
	5. Not suitable for pregnant or lactating females or those who are contemplating pregnancy within 90 days of the end of treatment.
	6. It is rapidly metabolized, and it fails to reach the necessary concentration levels in tissue and organs. Essentially, it has not been possible to get enough 2-DG into a patient and taken up by the critical tissue and organs in enough concentration to stop viruses.
	7. Literature shows that 2DG alone is usually non-effective and additional therapeutic agents are necessary.
	8. Adverse effects observed in 2DG-treated animal models, although undocumented in humans, still poses an area of concern.[26]
	9. Ultimately, any metabolic modifying drugs should be used with caution. Modulating glucose levels can have both beneficial and detrimental effects, especially on the brain, depending on the stage of viral pathogenesis.[15,26]

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Conflict of interest

The authors declare no conflicts of interest.

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