Target delivery of remdesivir may minimize the hepatotoxicity in COVID-19

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Abstract **- Remdesivir is a broad-spectrum antiviral agent meant to inhibit viral RNA polymerases against members of several virus families, including filoviruses. Although reported for significant clinical improvements in COVID-19, a detailed observation of the connection with the drawbacks of remdesivir therapy was poor pulmonary distribution and hepatotoxicity (transaminase elevation) was recorded that resulted in discontinuation of remdesivir therapy. Nanodrug delivery facilitates a large drug payload to the targeted site improving the efficacy. With the lesser dose administered, could be expected for minimized adverse events. Additional payload of ashwagandha will protect the liver from the damages caused if any. Remdesivir may be a safe and an effective therapeutic agent for COVID 19 when co-administered with ashwagandha as nanoparticles.**

Index Terms **- COVID-19; Hepatotoxicity; Remdesivir; Nanoparticle; Target delivery; Improved clinical outcome.**

BACKGROUND

The world is gearing up to battle against the Coronavirus disease 19 (COVID-19) outbreak which has already led to more than 362,483 deaths and 5,796,257 confirmed cases globally as on May 30, 2020 [1]. There are currently no approved effective therapeutic agents available for the treatment of COVID-19. National Institutes of Health (NIH), United States says it has begun a clinical trial testing the ability of Gilead's experimental drug remdesivir to treat people with COVID-19. The news comes at a crucial moment. Remdesivir is a prodrug of a nucleotide analogue that is intracellularly metabolized to an analogue of adenosine triphosphate that inhibits viral RNA polymerases. Remdesivir has broad-spectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses [2].

Remdesivir exhibited cell culture antiviral activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial (HAE) cells with a 50% effective concentration (EC50) of 9.9 nm. after 48 hours of treatment. The EC50 values of remdesivir against SARS-CoV-2 in Vero cells was 137 nm. at 24 hours and 750 nm. at 48 hours post-treatment [3, 4]. Many clinical studies have reported a significant clinical improvement with the transaminase elevations in the remdesivir clinical development program, including in healthy volunteers and patients with COVID19, without evidence of clinical hepatitis and elevated hepatic enzymes resulted in discontinuation of remdesivir therapy [5, 6]. As transaminase elevations have been reported as a component of COVID-19 in some patients, discerning the contribution of remdesivir to transaminase elevations in this patient population is challenging.

Following administration, drug is distributed to all the parts and that the total dose, rather than pulmonary distribution, is related to the clinical effect. A 10mg/kg intravenous dose given to cynomolgus monkeys distributes to the testes, epididymis, eyes, and brain within 4h with a limited pulmonary distribution [7].

Remdesivir for compassionate use is provided in two dosage forms, a solution formulation and a lyophilized formulation. However, selecting the optimal formulation for a drug is crucial to ensure its clinical and commercial success. Considering the frequency of liver dysfunction in patients with COVID-19, attribution of hepatotoxicity to either remdesivir or the underlying disease is challenging.

Detailed observation of the connection with the drawbacks of remdesivir therapy that poor pulmonary distribution and hepatotoxicity, nanodrug delivery of remdesivir co-administered with ashwagandha, an Indian herb reported for its hepatoprotective

potentials, could be an ideal choice to treat COVID-19 proving to be safe and effective.

Alveolar epithelial cells are an important target for coronavirus infection in the lung. In the alveolar region, the size of the particles appears to dominate the clearance rate. Micron scale particles between 1 μm and 5 μm are efficiently taken up by macrophages and Particles >6 μm are generally not phagocytosed but rather exhaled. Particles at the nanoscale (≤200 nm) can cross the cellular barrier independent of energy and are phagocytosed by macrophages [8]. This suggests that particles that are small enough can evade macrophage clearance when deposited in the deep lung. As a result, nanosized particles have ideal deposition characteristics for the delivery of remdesivir to alveolar regions of the lung to inhibit the viral RNA polymerase.

Drugs largely bypass metabolism when directly delivered into the lung and therefore a lesser dose of remdesivir is sufficiently enough if delivered right in the lungs to inhibit the viral RNA polymerase and this is possible only with targeted nanodrug delivery. The adverse events (low blood pressure, nausea, vomiting, sweating, increases in levels of liver enzymes) [3] noted with the loading dose of remdesivir 200mg once daily in patients, followed by a maintenance dose of 100mg once daily may be expected to minimize with an equivalent dose remdesivir and ashwagandha nanoparticle.

Attribution of hepatotoxicity to either remdesivir or the underlying disease is uncertain. To minimize the toxicity, remdesivir could be co-administered with Ashwagandha, an Indian herb known for its hepatoprotective potential [9].

CONCLUSION

To conclude, With the benefits of nano drug delivery that includes, nometric size permits drug delivery through impermeable barriers, large surface area to volume ratios for large drug payloads incorporation and improved efficacy, enhancing stability and bioavailability, increased specificity, improved antiviral delivery and controlled drug release to the target through engineered moieties, decrease the emergence of drug resistance, personalized therapy possibility, protection of the drugs and low adverse drug side effects, Remdesivir may be a safe and an effective therapeutic agent for COVID 19 when co-administered with ashwagandha as nanoparticle.

CONFLICT OF INTERESTS

The author(s) declare(s) that they have no conflict of interests

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