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Targeted, Site-Specific, Delivery Vehicles of Therapeutics for COVID-19 Patients. Brief Review

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Abstract

Definitive pharmacological therapies for COVID-19 have yet to be identified. Several hundred trials are ongoing globally in the hope of a solution. However, nearly all treatments rely on systemic delivery but COVID-19 damages the lungs preferentially. The use of a targeted delivery approach is reviewed where engineered products are able to reach damaged lung tissue directly, which includes catheter-based and aerosol-based approaches. In this review we have outlined various target directed approaches which include microbubbles, extracellular vesicles including exosomes, adenosine nanoparticles, novel bio-objects, direct aerosol targeted pulmonary delivery and catheter-based drug delivery with reference to their relative effectiveness for the specific lesions. Currently several trials are ongoing to determine the effectiveness of such delivery systems alone and in conjunction with systemic therapies. Such approaches may prove to be very effective in the controlled and localized COVID-19 viral lesions in the lungs and potential sites. Moreover, localized delivery offered a safer delivery mode for such drugs which may have systemic adverse effects.

Keywords

SARS-CoV-2, COVID-19, targeted drug delivery, local drug delivery, delivery vehicle, microbubbles, antivirals

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Introduction

Definitive COVID-19 therapies have yet to be identified, despite the many ongoing trials globally. The results based on early, small, underpowered, non-controlled studies and a few open label randomized-controlled trials (RCTs) have been discouraging. For example, one trial evaluating Lopinavir-Ritonavir for COVID-19 therapy, noted that an even higher dose than what was administered may be required to achieve therapeutic efficacy.[1] Only 2 pharmaceuticals have demonstrated signals toward efficacy. Remdesivir has been shown to reduce the total amount of time in ICU required per patient (Remdesivir for the Treatment of Covid-19 — Preliminary Report;J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. This article was published on May 22, 2020, at NEJM.org. DOI: 10.1056/NEJMoa2007764, and dexamethasone had reduced deaths by 35% in patients who needed treatment with invasive ventilation and by 20% in those needing supplemental oxygen (EU Clinical Trials Register: EudraCT 2020-001113-21

Clinical Trials.gov: NCT04381936).

However, almost all the proposed pharmaceutical therapies for COVID-19 pose at least a few possible adverse effects while citing the need for increased dosing. Targeted drug

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delivery of these promising pharmaceuticals might prove to be more effective, enhancing the local effect while attenuating their off-target side effects.[2] SARS-CoV-2 has an affinity for 2 host cell factors, which are primarily expressed in human lung tissue: ACE-2 and TMPRSS2.[3,4] Considering that COVID-19 primarily affects the lungs in patients with ARDS,[5] we propose a targeted drug delivery strategy using different types of drug delivery vehicles including microbubbles, extracellular vesicles (EV), nanoparticle drug carriers, liposomes, viral vectors, perfluorocarbon droplets, catheter-based and aerosol-based approaches. It should be noted that while there has been substantial research on local drug delivery vehicles in cancer and cardiovascular medicine, broadly; there appear to be only a handful of reports that describes using different carriers for targeted delivery in patients with COVID-19.[6-10] In the following, some of the newer approaches for targeted drug delivery in COVID-19 patients are discussed. It may also apply to other bacterial or viral pneumonias not associated with COVID-19.

Microbubbles

Microbubbles specifically have shown to adhere to sites of damaged vascular endothelium and thus may be a method of systemically targeting delivery of therapeutics to damaged lungs with SARS-CoV-2. For example, perfluoro butane gas microbubbles (PGMC) with a coating of dextrose and albumin efficiently bind to different pharmaceuticals. These 0.3 to 10 μm particles bind to sites of vascular injury.[5] Further, the perfluoro butane gas is an effective cell membrane fluidizer. The potential advantages of microbubble carrier delivery include none to minimal (additional) vessel injury through delivery, no resident polymer to degrade leading to eventual inflammation, rapid bolus delivery, and repeated delivery. Microbubble carriers were successfully used in different animal models and clinical trials to deliver antisense oligonucleotide and/or Sirolimus to the injured vascular bed.[11-13] The formulation of microbubbles and therapeutics is easy and could be performed in a hospital pharmacy, considering they are currently used widely to enhance diagnostic ultrasound imaging.[14] We propose to use microbubbles with pro-inflammatory cytokine (TNF-α, IL-1, or IL-6) inhibitors as an approach to mitigate the ARDS-induced cytokine storm. One possible drug is Tocilizumab, which is an IL-6 inhibitor, which shows some early promise as a possible COVID-19 therapeutic.[15,16] Tocilizumab may enhance the metabolism of drugs utilizing the cytochrome P450 system, which warrants further investigation into whether the same effects are attenuated or maintained when given locally versus systemically.[17,18]

Extracellular Vesicles (EV)

Kumar and colleagues describe the use of extracellular vesicles (EVs), which are a family of natural carriers in the human body.[9] EVs play a critical role in cell-to-cell communications and can be used as unique drug carriers to deliver protease inhibitors to treat COVID-19. Though the authors of the reported investigations concluded that certain limitations need to be overcome as well as understanding the mechanism to control targeted delivery. Specifically, the isolation and drug encapsulation techniques employed to engineer EVs could result in the loss of functional properties of the EVs, such as the destruction of surface proteins. These unintended changes could lead to nonspecific interactions with other cells, leading to off-target effects, toxicity, and suboptimal efficacy.[9]

Adenosine Nanoparticles

Recently, the efficacy in mitigating inflammation was demonstrated through the targeted delivery of adenosine and of multidrug formulations.[10] Bioconjugation of adenosine to squalene produces a prodrug-based nanocarrier, which, after nano formulation with Vit E, yields stable multidrug nanoparticles. This nanoparticle improves the bioavailability of both drugs with significant pharmaceutical activity in models of acute inflammatory injury. There are several clinical studies planned to use this technology in patients with COVID-19.[19]

Novel Bio-Objects

A group of researchers has succeeded in engineering a new kind of microscopic bio-object that may one day be used for personalized diagnostics and targeted delivery of drugs. The object consists of a genetically modified E. coli bacterium and nano-erythrosomes (small vesicles made of red blood cells), and it demonstrates a substantial improvement in motility over previous designs.[20]

Direct Pulmonary Delivery

Direct pulmonary delivery (e.g., aerosol, inhalers, etc.) is a more selective mode of drug delivery that typically requires a lower quantity of drug to achieve an effective dose. Currently, 2 studies are enrolling patients to study the feasibility and efficacy of this approach — the NOSARSCOVID Phase II Trial (NCT04306393) and the Pulsed Inhaled Nitric Oxide for Treatment of Patients with Mild or Moderate COVID-19 Expanded Access Program (NCT04358588). Pulmonary drug delivery can provide the following advantages: quick onset of action coupled with ease and convenience of administration; the pulmonary dose is significantly lower than the oral dose; and degradation of the drug in the liver can be avoided. On the other hand, the following drawbacks are often associated with pulmonary drug delivery: improper dosing, stability problems, and difficulty in producing the optimum particle size. In addition, not all drugs can be delivered via a pulmonary route due to formulation difficulties. Given that acoustically activatable perfluoro propane droplets permeate across endothelial barriers to reach the interstitial spaces and even intracellular locations.[9] This may be an ideal method of enhancing nitric oxide delivery to regions of abnormal ventilation to perfusion mismatch in COVID-19 pneumonia. However, it should be noted that

inhaler-based delivery is an aerosol-generating procedure and therefore and it should be performed with extreme caution and the appropriate personal protective equipment (PPE).

Heparin and low-molecular weight heparin have been used in the anticoagulant management of COVID-19. Heparin also exhibit antiviral properties and localized delivery in the lung may have therapeutic effects including both the antiviral and anticoagulant effects. The inhaled formulations of heparins have been reported before in animal models such as dogs.[21] Special devices such as jet and ultrasonic nebulizers have also been used to deliver heparin to intrapulmonary sites.[22] A recent article has reported on the intrapulmonary delivery of heparin in COVID-19 patients and call for randomized clinical trial to validate the clinical efficacy of this approach.[23] Localized delivery of heparin may also results in anti-inflammatory, cytoprotective and membrane stabilizing effects. Other modalities may include heparin mist in different formulations to produce eco effects.

Catheter-Based Drug Delivery

Catheter-based local drug delivery of antivirals (liquid remdesivir) and/or pro-inflammatory cytokine inhibitors (tocilizumab) can be performed trans-pulmonary, with a Swan-Ganz catheter. The drug can be administered through the pulmonary artery to target pulmonary vasculature, which is safe and feasible. This does not require imaging and could be performed bedside. Another aspect recently revealed is the prothrombotic state in some COVID-19 patients. Systemic antithrombotic and thrombolytic therapy has been anecdotally used with scattered reports of acute improved oxygenation. Therefore, catheter-directed thrombolysis could be another approach through localized thrombolysis. Another approach is the recently, commercially available intravenous microbubbles, which has been utilized for ultrasound-targeted sonothrombolysis in acute myocardial infarction and in pulmonary thromboembolic disease.[6,7] The mechanism for sonothrombolysis appears to be cavitation induced thrombus dissolution in addition to vasodilation induced by endothelial shear-release of nitric oxide.[8]

Conclusion

Given the growing evidence that the most detrimental SARS-CoV-2 reactions are primarily within the respiratory system, localized targeted delivery of therapeutics may prove advantageous over a systemic approach, provided that bioavailability to the target tissue can be proven/verified. Several approaches have been discussed, in which microbubbles are the only carrier to have been used in clinical practice and therefore are the most promising. Adenosine nanoparticles and novel bioobjects are other classes of drug carriers under either preclinical development or in early clinical investigation. Beyond carriers, there are several delivery methods to also consider. For example, direct inhalation or pulmonary delivery are a highly selective modes requiring less dosage, and there are several ongoing trials and expanded access programs to evaluate this approach. Finally, there are several catheter-based drug delivery approaches, including catheter-directed thrombolysis to treat viral coagulopathies (pulmonary embolism, micro-thrombosis) induced by SARS-CoV-2 infection. The nebulized drug delivery systems provide a practical and clinically feasible approach for the localized delivery of heparins and other drugs in the management of pulmonary lesions with high viral load. Further investigations through well-designed, timely clinical studies for targeted site-specific therapy will demonstrate evidence toward the best carriers, delivery methods, and approach (i.e. combination systemic and local delivery versus stand-alone).

Author Contribution

All authors equally contributed to the work in this manuscript.

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