

A brief note on the scope of RNA interference (RNAi) therapy in mitigating COVID-19

Abstract

Together with the use of number of repurposed/ repositioned antiviral drugs and immunomodulatory agents against the severe acute respiratory coronavirus 2 (SARS-CoV-2) infection, currently several vaccines are under human trials to mitigate the COVID-19 worldwide. Although the drugs and vaccines appear to be effective in maximum cases or trials; however, the associated side effects, the required induction of the long-lasting immunity, and finally, the safety concerns are of significance in terms of their consistent application/ administration. A vast research on the SARS-CoV-2 genomics and on its similarities with SARS-CoV-1 and with the Middle East Respiratory Syndrome coronavirus (MERS-CoV) have unravelled the viral avoidance of the host immunity which creates a challenge in course of effective vaccine development although several COVID-19 vaccines are currently being used commercially worldwide. Such an unsteady circumstance led the scientists also to think on a new remedial approach i.e., the RNA interference (RNAi) therapy to inhibit the SARS-CoV-2 proliferation by degrading the viral RNAs. Present review discussed such strategy and its effectiveness during the ongoing COVID-19 pandemic.

Keywords: COVID-19 pandemic, SARS-CoV-2, drugs, vaccines, RNAi therapy

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Introduction

COVID-19 pandemic has been displaying devastating impact on the global public health since the end of December, 2019 already resulting in 2,951,832 deaths out of 136,996,364 infected cases so far.¹ The viral agent causing this pandemic, the severe acute respiratory virus 2 (SARS-CoV-2), has quite similarity in terms of the genomic organization as well as the mode of pathogenesis to the earlier coronavirus strains; i.e., the severe acute respiratory syndrome coronavirus 1 (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS).²⁻⁴ SARS-CoV-2 is known to get entry into the nasopharyngeal tract from the respiratory droplets, and spread along the bronchial tubes lining the lungs, making the lungs mucous membrane inflamed and hard resulting in difficulty in oxygen supply to the blood, ultimately causing the shortness in breathing.^{3,5-7} The viral spike (S) glycoprotein subunit S1 receptor binding domain (RBD) interrelates the host surface angiotensin converting enzyme 2 (ACE-2) receptors, and the membrane fusion subunit S2 then fuses the host and viral membranes, releasing the viral RNA into the host cells as well instigating both innate- and adaptive immunity within the host together with the generation of cytokine storm with the concomitant avoidance of the host protective immunity by the virus.^{3,7,8}

In order to fight against COVID-19, an array of research has been conducted for more than a year; and several drugs and vaccines have been designed which apparently got success in mitigating the disease. However, there are cases of failure and side effects of the administration of these drugs and vaccines. Therefore, scientists are also thinking on therapeutic strategies alternative to the antiviral drugs and vaccines. Present review briefly discussed on a new approach named as RNA interference (RNAi) therapy to alleviate the ongoing COVID-19 pandemic.

Drugs and vaccines currently used against SARS-CoV-2

In search of active drugs for treating COVID-19, the *in silico* drug design, cell culture models and the clinical trials showed

several repurposed drugs to be promising of which remdesivir has been approved by the U.S. Food and Drugs Administration (FDA) as the authorized drug for the emergency use.⁵ However, other antiviral drugs and immunomodulatory agents like ribavirin (which was also used for the treatment of SARS and MERS patients), favipiravir, cefuroxime, hydroxychloroquine, lopinavir, ritonavir, arbidol, ostalmovir, and even dexamethasone have been found to be useful.^{5,9} For the quick treatment, the convalescent plasma therapy has appeared as another effective method.¹⁰ However, the most accepted treatment strategy is the vaccination on which scientists are rigorously working around the world.¹¹ Among the currently commercially used vaccines, the Pfizer-BioNTech (BNT162b1) and Moderna (mRNA 1273) vaccines, the prophylactic DNA vaccine, INO-4800, the viral vector vaccine, ChAdOx1 nCoV-19 (Oxford/ AstraZeneca) are worth to note.¹¹⁻¹⁴ Among others, the JNJ-78436735/ Ad26.COV2.S (Johnson&Johnson) vaccine, the NVX-CoV2373 (Novavax) vaccine, BBIBP-CorV (Sinopharm) vaccine, the BBV152/ Covaxin, are also good candidate vaccines.¹⁵

Rationale of RNAi therapy application

Appropriate vaccination usually excites the required immune responses within the host. However, the manifestation of the SARS-CoV-2 variants ensuing from the mutations within the viral spike (S) protein (serving as the main target for the neutralizing immunoglobulins) may render the vaccines apparently questionable; and it must be noted that even minor mutations may cause the virus to be effective in escaping the host protective immunity even the vaccines have been administered.^{11,16,17} Keeping these limitations of the currently used drugs and vaccines, scientists are also working on some other substitutes of which one is the RNAi therapeutic strategy.^{11,18,19}

Inauguration of RNAi therapy as the antiviral strategy

To diminish the COVID-19 pandemic, along with the ongoing efforts using the CP therapy, drugs and vaccines, the innate RNA

interference (RNAi) therapy (which silences the desired gene expression by degrading the corresponding mRNA) appeared to be interesting which facilitates specific binding and silencing of the therapeutic targets by employing the short interfering RNA (siRNA: 19–27 bp double-stranded RNAs) and the short hairpin RNA (shRNA, produced *in silico* through the plasmid DNA expression vector) molecules.^{18,19} Indeed, besides the usage of drugs and vaccines, the molecular groundworks on the RNAi agents together with the hopeful viral targets and the host factors with the possible modulation of the host protective immunity by (regulating the protein synthesis events) have been described previously with the comparative analysis of various platforms; and it is to be noted that the siRNAs can be distributed to the cytosol to occupy the RNA-induced silencing complex (RISC) in the host cells.¹⁹ However, according to Uludağ et al., 2020, mounting the RNAi based drugs against SARS-CoV-2 may be a longer procedure compared to that of the development of the already approved re-purposed drugs.¹⁹

RNAi therapy to mitigate COVID-19 can be directed against either against the viral proteins required for viral replication, or towards the host factors engaged in the viral transmission within cell to cell.¹⁹ The RNAi-provoked silencing actually interferes

- i. With the SARS-CoV-2 life cycle by hindering the expression of the ACE-2 receptor thereby snooping the viral entry (mediated by the microRNA miR-1246);
- ii. With its non-structural protein 15 (nsp15), and the ORF-3a and ORF-4a whose products facilitate the viral release, The control of the cytokine storm; and
- iii. Most importantly, such therapy targets the ORF-9b whose products work as the interferon (IFN) agonist (this is to be noted that IFN creates the anti-viral state).^{6,11,18,19}

Conclusion

The possible application of RNAi agents for the management of COVID-19 can be fruitful in future although it's known that for mitigating viral infection, appropriate vaccination is the most acceptable strategy. Besides the currently used repurposed drugs, the RNAi therapy could augment the overall therapeutic concept. Since, the immunizations through vaccination may not be lasting or effective for some individuals, such therapy may then bring new hope to cure the disease. However, till date any therapeutic RNAi therapy has not been reported to silence the SARS-CoV-2 target proteins; and hence more studies together with clinical trials are required to bring an effective conclusion about the future perspectives of the RNAi therapy.

Competing interests

Authors declare that they have no conflict of interest.

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