Editorial

Nuclear Medicine Communications

A theranostic approach based on radiolabeled antiviral drugs, antibodies and CRISPR-associated proteins for early detection and treatment of SARS-CoV-2 disease

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Nuclear Medicine Communications 2020, 41:837–840

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Received 27 May 2020 **Accepted** 4 July 2020

The recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) is now a major public health issue that raised an international emergency situation and serious concern as recognized by the WHO [1]. SARS-CoV-2, an enveloped single-stranded RNA beta-coronavirus, is a highly contagious virus with a high mortality rate, particularly in people with immunocompromised conditions [2]. Most COVID-19 patients present with fever, cough and respiratory symptoms, and a fraction requires mechanical ventilation. Based on some reports, the rate of death in such patients may be up to 10% [3]. In addition, subjects without clinical symptoms may serve as sources of transmission.

The first line for detecting of SARS-CoV-2 is a real-time reverse transcription PCR (rRT-PCR) test, though it suffers from some limitations, such as variations in the positive rate and sensitivity in different types of clinical specimens, such as Bronchoalveolar lavage fluid, sputum, nasal swabs, fibrobronchoscope brush, pharyngeal swabs, feces and blood [4], low universal availability and lengthy time of detection [5]. On the other hand, computed tomography (CT) has shown promising results in the detection, diagnosis and management of COVID-19 [6]. However, this imaging modality is not feasible for early detection and diagnosis of COVID-19, and some studies indicated no CT findings in these patients. Other imaging modalities, such as chest radiography [7], ultrasound [8] and PET [9,10], have also been evaluated, but they have not been used as the first-line diagnostic test. However, a study by Polverari *et al.* [11] observed the presence of bilateral, diffuse and intense ^{18}F-FDG uptake in the lower lobes in asymptomatic COVID-19 patients referred for PET/CT-based restaging of non-small cell lung cancer [11]. In this case, active inflammatory processes were reported by radiologists, while the CT pattern was highly suspicious for ongoing COVID-19 pneumonia and there were no other clinical symptoms. COVID-19 was confirmed later by rRT-PCR in this patient. In addition, Albano *et al* [12]. reported that PET/CT is an appropriate modality for detecting COVID-19 in asymptomatic patients. In addition, the role of nuclear medicine in COVID-19 is elaborated by Juengling *et al.* [13].

As a critical issue, there are no specific treatments for COVID-19, though a number of experimental antivirals and existing drugs targeting other viruses are being tested. In addition, medical care is provided to relieve and treat the symptoms of the disease. Several drugs, such as type 1 interferon (IFN-I), chloroquine, ivermectin, aerosolized α-interferon, lopinavir, ritonavir, ribavirin, remdesivir, darunavir, mAb targeting PD-1 (Camrelizumab) and IL6 (Tocilizumab) alone or in combinations have been tested resulting in variable outcomes in different patients [14–16]. In addition, a wide range of in-vitro, in-vivo, in-silico and clinical trials are in progress to find the best matches.

Molecular imaging techniques, including planar gamma camera (scintigraphy) or 3D single-photon emission computed tomography (SPECT) and PET, employ short-lived radiolabeled tracers to characterize and visualize biochemical and molecular processes of disease *in vivo*. Various radionuclides are commonly used for viral infection imaging. In addition, radionuclides with favorable characteristics are used in the treatment of a wide range of diseases. Some of these studies indicated the feasibility of this therapy for viral infections [17]. On the use of PET/CT for the management of bacterial infectious diseases, Tucker *et al.* [18] applied an interesting approach. In this animal study, pharmacokinetic models were developed by using dynamic ^{11}C-rifampin PET/CT to study intralesional antimicrobial distribution in tuberculous meningitis.

In the present work, we propose a theranostic approach based on radiolabeled antiviral drugs, antibodies and clustered regularly interspaced short palindromic repeats (CRISPR)-associated proteins for early detection and

DOI: 10.1097/MNM.0000000000001269

treatment of SARS-CoV-2 disease. This approach is composed of components constituting a unique approach, including the use of theranostic radionuclides, radionuclide-based imaging and antiviral drugs/antibodies and CRISPR-associated proteins.

Theranostic radionuclides are the key components of the proposed approach. These radionuclides emit radiation that could be used for imaging and treatment. Several radionuclides in combinations with monoclonal antibodies or antiviral drugs have been used for treatments of viral infections or inflammation. Radioimmunotherapy of infections induced by viruses such as HIV, HSV and HPV has been reported in the literature [19–21]. Conversely, some studies have suggested and applied low-dose radiation to treat pneumonia or other inflammatory diseases [22,23]. Calabrese *et al.* [24] pointed out the capacity of low doses of radiographs to suppress inflammatory responses in treating pneumonia based on some historical studies that applied radiation to treat pneumonia during the first half of the 20th century. Recently, low-dose radiation therapy was proposed as a new treatment strategy for COVID-19 [25]. The main mechanistic basis is that low levels of radiation can induce anti-inflammatory responses, such as decreasing levels of proinflammatory cytokines like IL-1β or inhibiting leukocyte recruitment. As such, an absorbed dose of 30–100 cGy of radiation delivered to the lungs of patients with COVID-19 pneumonia may result in the reduction of inflammation. Ghadimi-Moghadam *et al.* [26] introduced a modified treatment method for COVID-19 patients based on a single dose of 100, 180 or 250 mSv of radiograph radiation. They claimed that these doses could modulate excessive inflammatory responses, regulating lymphocyte counts and controlling bacterial co-infections in patients with COVID-19.

In our proposed radiation-assisted treatment, a wide range of radiation doses could be delivered to the infected regions locally and specifically by using antibodies or antiviral drugs. Radiation emitted from radionuclides will act in three ways: direct-hit, cross-fire and immunomodulation. Radiation destroys the infected cells and disables the virus through the first two effects, whereas radiation triggers fundamental antiviral immune parameters, such as natural killer cells and interferon production to cope with the viral functions, through the immunomodulation effect. A number of theranostic radionuclides are commercially available and used mostly for cancer treatment. Yet, they could also be used in viral infectious diseases. For example, ^{68}Ga-^{90}Y or ^{68}Ga-^{177}Lu pairs are theranostic radionuclides employed for various applications [27]. In addition, ^{64}Cu, ^{83}Sr, ^{86}Y, ^{124}I and ^{152}Tb could be used in the clinical setting [28].

Although there is no specific antibody or drug for radiolabeling and targeting the infected regions, several potential antiviral/antibodies are available for early phase studies. Previous antiviral drugs/antibodies that have been investigated for the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS-CoV could be tested. It should be noted that the target receptors on the host cell surfaces are different for these viruses that should be taken into account for drug administration. Based on previous studies, angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase-4 (DPP4) are target receptors for SARS-CoV and MERS-CoV, respectively [29]. In this light, anti-ACE2 mAbs may be feasible choices. In addition, other inhibitors such as peptidic fusion inhibitors and protease inhibitors could be examined. Because the host receptor for SARS-CoV is similar to SARS-CoV-2 (ACE2), the treatments for SARS-CoV can be extrapolated for use in SARS-CoV-2. In addition, the spike protein located on the viral membrane responsible for virus entry; hence inducing host immune response is a key potential target for developing new antiviral drugs. Table 1 summarizes some potential antibodies and antiviral drugs previously investigated as potential therapeutic approaches for SARS-CoV. These drugs may be potentially labeled with theranostic radionuclides.

CRISPR and the associated proteins (Cas) system is a powerful tool for cellular DNA genome editing. The endonuclease activity as an adaptive immune system in prokaryotes is nowadays accepted as a popular tool to develop a wide range of clinically significant drugs including antivirals [30]. Recently, comprehensive viral research studies have focused on CRISPR-Cas based antiviral strategies against HIV-1, HPV-B, EBV, HSV and HCV [31,32]. More recently, CRISPR-Cas has been suggested for the diagnosis and treatment of SARS-COV-2 [33,34]. However, the potential of this approach for the management of COVID-19 remains to be assessed in preclinical and clinical settings. The platform, called specific high-sensitivity enzymatic reporter unlocking (SHERLOCK), a portable and ultrasensitive CRISPR-based tool for the detection of RNA or DNA from clinically relevant samples, may be valuable for COVID-19 detection [35]. In addition, CRISPR-associated proteins could be labeled with radionuclides for improved detection, tracking and treatment of COVID-19. Furthermore, by radiolabeling the CRIPR Cas proteins, the biological behavior of SARS-COV-2 in living systems could be elaborately studied.

To image radiolabeled antiviral/antibody drugs or CRISPR proteins with theranostic radionuclides, a molecular imaging modality is needed. This could be either planar scintigraphy, or 3D imaging modalities of SPECT or PET [36]. The selection of the optimal modality is dictated by the type of the radionuclide, associated costs and the need for deployment in a larger population. The imaging system detects photons emitted from the radionuclides and converts them to visible images or numbers

Table 1 Summary of studies reporting on the use of various antiviral drugs and antibodies investigated as potential agents for the treatment of SARS-CoV

Drug name	Type	Mechanism of action	References
S230	mAb	Blocking spike protein subunits and ACE2 cellular receptor	[40]
CR3014	mAb	Blocking spike protein subunits and ACE2 cellular receptor	[41]
80R	mAb	Blocking spike protein subunits and ACE2 cellular receptor	[42]
4D4	mAb	Inhibiting the postinteraction in the viral penetration	[43]
F26G19	mAb	Blocking spike protein subunits and ACE2 cellular receptor	[44]
Type 1 interferons	Cytokine	Slowdown of cell metabolism and Adaptive immunity	[14]
Remdesivir	Antiviral drug	Inhibiting viral RNA polymerase action	[16]
Lopinavir	Antiviral drug	Protease inhibitor	[16]
Emetine	Antiprotozoal	Protein synthesis inhibitor	[16]
Homoharringtonine	Anticancer	Protein synthesis inhibitor	[16]
Chloroquine	Antimalarial/antiviral	Increases late endosomal and lysosomal pH	[15]
Ivermectin	Antiparasite/antiviral	Cell hyperpolarization	[45]

ACE2, angiotensin-converting enzyme 2.

(quantified). They have to provide high-quality images in terms of the signal-to-noise ratio [17]. On the other hand, the main components of the imaging systems including collimators, detectors and image processing software also should have dedicated designs to quantify minimum levels in radioactive regions of the infected areas for early diagnosis of the disease.

Another important aspect of our proposed approach is the evaluation and understanding of the pathogenesis of COVID-19. Based on experience and knowledge gathered from previous SARS-CoV and MERS-CoV studies, molecular imaging modalities could play critical roles in fostering understanding of complex mechanisms of diseases. In previous studies, the immune response to MERS-CoV was studied by PET/CT [37], whereas other studies used PET/CT to quantify lung infection, the inflammatory burden of disease, and responses to anti-inflammatory therapies [38]. Chefer *et al* [39] inserted a SPECT/CT compatible reporter gene into MERS-CoV to demonstrate that a functional SPECT/CT reporter gene can be inserted into a virus. We herein suggest radiolabeled drugs, antibodies and CRISPR/Cas proteins as theranostic and active agents for the treatment and understanding of COVID-19.

In conclusion, the proposed approach could be investigated to treat and track the treatment of COVID-19 in the early phases. This approach is based on the use of theranostic-radiolabeled antiviral drugs, antibodies and CRISPR-associated proteins. Further preclinical and clinical studies are needed to examine the feasibility of this strategy. Although the role of molecular imaging modalities is not fully investigated, few published reports seem to suggest that PET/CT could be used for early detection. Furthermore, therapeutic delivery and tracking of radiolabeled drugs and the study of mechanisms of pathogenesis could be of significant interest using molecular imaging and theranostics.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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