Journal of Nuclear Medicine, published on April 17, 2020 as doi:10.2967/jnumed.120.246611

The role of Nuclear Medicine for COVID-19 – Time to act now.

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Sir,

As every medical department worldwide is bracing for the impact the corona virus disease 2019 (COVID-19) pandemic will pose on daily routines, the scientific community starts to excel in exploring the different facets this novel disease bears for prevention, diagnosis and treatment. Nuclear medicine, touting itself “molecular medicine” as well as “theranostic medicine” may not fall short here, as we have much to offer.

While it may be wise for individual nuclear medicine departments to focus on taking precautions for themselves and their most vulnerable patients, suffering from oncological and

cardiovascular or neurological “predispositions”, to the risks of exposure to COVID-19 bearing individuals (*1*) , we should still motivate ourselves and the academic nuclear medicine community to actively participate in improving care for COVID-19 patients.

Accumulating evidence suggests that some of the detrimental effects seen in patients with severe COVID-19 is attributed to an overly host antiviral defense as seen in severe acute respiratory syndrome (SARS), leading to hyperinflammatory reactions or cytokine storm syndrome, sometimes also affecting the CNS (*2*,*3*).

Until now, however, existing knowledge regarding supportive care and adjunctive pharmacologic therapy is limited. Even worse, a subgroup of COVID-19 patients that seems to do well after getting out of the intensive care unit, dies of acute respiratory syndrome just several days later, without clinical signs indicating their imminent deterioration. This situation may be one of the first places where nuclear medicine should tune in: With FDG-PET/CT for decades being well evaluated for its sensitivity in detecting inflammatory disease (for review: (*4*)), we should start to prospectively collect data in a well defined group of patients at given time intervals during the course of COVID-19 infection to better understand the inflammatory component of the disease and may be find early prognostic signs that warrant proactive anti-inflammatory treatment in patients at risk. Until now, only anecdotal data exists (*5*). As a nuclear medicine community, we ought to team up and establish protocols suitable for multicentric evaluation as soon as possible, meeting the requirements for controlled trials. Serial exams should include both, cohorts of patients with proven COVID-19 with different severity and extended follow-up after recovery, as well as symptomatic patients with radiographic findings typical for COVID-19, but without initial proof of infection and should not

only focus on pulmonary inflammation but also address possible inflammatory involvement e.g. of myocard, pericard, vasculature, muscles, intestine and the CNS.

At academic sites providing of research facilities including cyclotron and radiopharmacy production, the research into the inflammatory cascade could go even further. There are well-established radiopharmaceuticals suitable as inflammatory biomarkers at an intracellular level, e.g. targeting the purinergic P2X7 receptor (*6*). While initially designed to quantify neuroinflammation, they can easily be repurposed for imaging the inflammosome and quantifying inflammation at a whole-body-level. As there are also potential P2X7-inhibitors at receptor level (*6*), showing anti-inflammatory effects in animal models (*7*), translational research may here form the rationale for anti-inflammatory therapy principles in COVID-19. Furthermore, nuclear medicine has the potential to provide evidence and clarify contradictory concepts in the use of nonsteroidal anti-inflammatory drugs in COVID-19, where clinicians have to state “many clinical anecdotes remain stalled in biological plausibility” (*8*), by directly depicting cyclooxygenase-2 (COX2)-involvement using established COX2-inhibitory radiopharmaceuticals (*9*).

Possible repurposing of other established radiopharmaceuticals to investigate COVID-19 specific pathomechanisms might target the cytokine signaling pathway (e.g. chemokine receptor CXCR4, interleukin IL-6), fibroblast activation protein inhibitors (FAPI), to address postinflammatory fibrosis, or inhibitors of the type 1 angiotensin-II-receptor ATR1 (e.g. KR31173), involved in cellular internalization of SARS-CoV-2 (*2*). Development of novel radiopharmaceuticals could also focus on directly targeting the entry receptor for SARS-CoV-2, the angiotensin-converting-enzyme-2 (ACE2). Radiolabeling of an ACE2-receptor antagonist has already been achieved for

receptor autoradiography protocols (*10*), and could serve as starting point for PET tracer development, increasing our readiness for the next corona virus shift.

The recent WHO initiative of creating a voluntary intellectual property pool for COVID-19 products to balance intellectual property and accessibility could address some of the issues inhibiting broader application of new tracers. Regulatory agencies also recently have shown extraordinary performance in overviewing new applications. And nuclear medicine already has proven in many ways to excel in logistics for radiopharmaceutical distribution, partnering with academic, administration and industrial stakeholders.

The examples chosen here are not meant to be comprehensive. They are meant to stimulate our community's potential to contribute to one of the biggest challenges in modern medicine. The existing SNMMI connect platform may serve as a natural vehicle to collectively define and distribute protocols suitable for multicentric trials and to share what it needs for making novel radiopharmaceuticals accessible at an accelerated time scale.

Let us build a network of clinical trials, let us start now and fast and bold. It is time to act now.

Conflict of interest

No potential conflicts of interest relevant to this article exist

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