Received: 25 February 2020 | Accepted: 27 February 2020

DOI: 10.1002/ddr.21656

COMMENTARY

DDR WILEY

Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics

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Abstract

At the time of writing this commentary (February 2020), the coronavirus COVID-19 epidemic has already resulted in more fatalities compared with the SARS and MERS coronavirus epidemics combined. Therapeutics that may assist to contain its rapid spread and reduce its high mortality rates are urgently needed. Developing vaccines against the SARS-CoV-2 virus may take many months. Moreover, vaccines based on viral-encoded peptides may not be effective against future coronavirus epidemics, as virus mutations could make them futile. Indeed, new Influenza virus strains emerge every year, requiring new immunizations. A tentative suggestion based on existing therapeutics, which would likely be resistant to new coronavirus mutations, is to use available angiotensin receptor 1 (AT1R) blockers, such as losartan, as therapeutics for reducing the aggressiveness and mortality from SARS-CoV-2 virus infections. This idea is based on observations that the angiotensin-converting enzyme 2 (ACE2) very likely serves as the binding site for SARS-CoV-2, the strain implicated in the current COVID-19 epidemic, similarly to strain SARS-CoV implicated in the 2002–2003 SARS epidemic. This commentary elaborates on the idea of considering AT1R blockers as tentative treatment for SARS-CoV-2 infections, and proposes a research direction based on datamining of clinical patient records for assessing its feasibility.

KEYWORDS

angiotensin-converting enzyme 2 (ACE2), AT1R blockers, COVID-19 epidemic, losartan, SARS-CoV-2

At the time of writing this commentary (February 2020), the death toll from the COVID-19 epidemic caused by coronavirus SARS-CoV-2, which emerged in late December 2019 in Wuhan, China (World Health Organization, 2019), has surpassed the combined death toll of the SARS (Severe Acute Respiratory Syndrome) epidemic of 2002–2003 and the MERS (Middle East Respiratory Syndrome) epidemic of 2013 combined (Mahase, 2020). This epidemic seems to be spreading at an exponential rate, with a doubling period of 1.8 days, and there are fears that it might progress to pandemic scales (Cheng & Shan, 2020). Yet, no SARS-CoV-2 therapeutics are presently available, albeit some treatment options which await validation have been published, including several broad spectrum antivirals such as favipiravir and remdesivir (Beigel et al., 2019, Li & De Clercq, 2020), the anti-malaria drug chloroquine (Gao, Tian, & Yang, 2020), and a traditional Chinese herbal formula (Luo et al., 2020). The ultimate solution is, obviously, developing a SARS-CoV-2 vaccine (Patel et al., 2020; Zhang & Liu, 2020). However, vaccines for the SARS-CoV developed since its outbreak 18 years ago have not materialized to an approved product. This topic has been reviewed in detail (de Wit, van Doremalen, Falzarano, & Munster, 2016) and is beyond the scope of this brief commentary. In addition, there have been concerns about vaccine-mediated enhancement of disease, for example, due to pulmonary immunopathology upon challenge with SARS-CoV (Tseng et al., 2012). Moreover, even once a vaccine is approved for human use, high virus mutation rates mean that new vaccines may need to be developed for each outbreak, similarly to the situation with new annual influenza vaccines (Belongia et al., 2017). Below, I describe an alternative option which, if proven to be effective, would allow a rapid application in the clinic.

A recent hypothesis suggested that angiotensin receptor 1 (AT1R) inhibitors might be beneficial for patients infected by COVID-19 who experience pneumonia (Sun, Yang, Sun, & Su, 2020). This article, however, is only available in Chinese with an English abstract that does not describe its logic besides the notion that the renin–angiotensin system is dysregulated by SARS-CoV-2. A similar suggestion proposing the treatment of COVID-19 patients with AT1R blockers was put forward in a "rapid online response" posted online by the *British Medical Journal* on February 4, 2020 (Phadke & Saunik, 2020). These tentative suggestions were based on the observation that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the receptor binding domain for its spike protein (Lu et al., 2020; Wan, Shang, Graham, Baric, & Li, 2020), similarly to the coronavirus strain implicated in the 2002–2003 SARS epidemic (Dimitrov, 2003; Ge et al., 2013; Li et al., 2003; Prabakaran et al 2004; Turner, Hiscox, & Hooper, 2004). Moreover, the receptor binding domains of these two coronaviruses share 72% amino acid sequence identity, and molecular simulation has indicated similar ternary structures (Chen, Guo, Pan, & Zhao, 2020). However, SARS-CoV-2 includes a distinct loop with flexible glycyl residues replacing rigid prolyl residues in SARS-CoV, and molecular modeling indicated that the receptor binding domain of SARS-CoV-2 has higher affinity for ACE2 compared with SARS-CoV (Chen et al., 2020).

Notably, angiotensin-converting enzyme (ACE) and its close homologue ACE2, while both belonging to the ACE family of dipeptidyl carboxydipeptidases, serve two opposing physiological functions. ACE cleaves angiotensin I to generate angiotensin II, the peptide which binds to and activates AT1R to constrict blood vessels, thereby elevating blood pressure. By contract, ACE2 inactivates angiotensin II while generating angiotensin 1–7, a heptapeptide having a potent vasodilator function via activation of its Mas receptor (Santos et al., 2003), and thus serving as a negative regulator of the renin–angiotensin system. These opposing actions of ACE and ACE2 were recently reviewed by Smyth, Cañadas-Garre, Cappa, Maxwell, & McKnight, 2019.

The AT1R antagonists losartan and olmesartan, commonly applied for reducing blood pressure in hypertensive patients, were shown to increase cardiac ACE2 expression about three-fold following chronic treatment (28 days) after myocardial infarction induced by coronary artery ligation of rats (Ishiyama et al., 2004). Losartan was also shown to upregulate renal ACE2 expression in chronically treated rats (Klimas et al., 2015). In agreement with these observations, higher urinary ACE2 levels were observed in hypertensive patients treated with the AT1R antagonist olmesartan (Furuhashi et al., 2015). Taken together, these observations suggest that chronic AT1R blockade results in ACE2 upregulation in both rats and humans.

As described above, ACE2 is the common binding site for both the SARS-CoV of the 2002–2003 SARS epidemic and, most likely, also the SARS-CoV-2 strain underlying the current COVID-19 epidemic. Hence, the suggestion to treat SARS patients with AT1R antagonists for increasing their ACE2 expression seems counterintuitive. However, several observations from studies on SARS-CoV, which very likely are relevant also for SARS-CoV-2, seem to suggest otherwise. It has been demonstrated that the binding of the coronavirus spike protein to ACE2, its cellular binding site, leads to ACE2 downregulation, which in turn results in excessive production of angiotensin by the related enzyme ACE, while less ACE2 is capable of converting it to the vasodilator heptapeptide angiotensin 1–7. This in turn contributes to lung injury, as angiotensin-stimulated AT1R results in increased pulmonary vascular permeability, thereby mediating increased lung pathology (Imai et al., 2005; Kuba et al., 2005). Therefore, higher ACE2 expression following chronically medicating SARS-CoV-2 infected patients with AT1R blockers, while seemingly paradoxical, may protect them against acute lung injury rather than putting them at higher risk to develop SARS. This may be accounted for by two complementary mechanisms: blocking the excessive angiotensin-mediated AT1R activation caused by the viral infection, as well as upregulating ACE2, thereby reducing angiotensin production by ACE and increasing the production of the vasodilator angiotensin 1–7. These aspects on the role of dysregulated ACE2 in SARS-CoV pathogenesis are reviewed in detail by de Wit et al., 2016. Incidentally, following the SARS-CoV epidemic of 2002–2003, ACE2 inhibitors were suggested as SARS therapeutics (Huentelman et al., 2004; Turner et al., 2004); however, this proposal has not led to new drugs.

Incidentally, in the context of the human immunodeficiency viruses (HIV), it has been demonstrated that higher expression levels of the HIV binding sites CCR5 and CD4 protect from, rather than increase, HIV virulence. Michel et al. reported that HIV employs its early gene Nef product for avoiding superinfection during the viral-entry step by downregulating CCR5. This Nef-mediated downregulation enhances the endocytosis rate of both CCR5 and CD4, which in turn facilitates efficient replication and spread of HIV, thereby promoting AIDS pathogenesis (Michel, Allespach, Venzke, Fackfmicheller, & Keppler, 2005). It remains to be studied if a comparable mechanism for avoiding superinfection has evolved in coronaviruses; in which case, the suggestion of applying AT1R blockers as SARS therapeutics, even that they upregulate the expression of the ACE2 virus binding site, will not seem paradoxical.

Losartan, telmisartan, olmesartan (and additional AT1R antagonists) are widely applied in the clinic since the 1990s for control of hypertension and kidney disorders, and are known as safe drugs that are rarely implicated in adverse drugs events (Deppe, Böger, Weiss, & Benndorf, 2010; McIntyre, Caffe, Michalak, & Reid, 1997). However, it should be noted that around half of SARS-CoV patients developed hypotension during their hospitalization (Yu et al., 2006). At time of writing this commentary, no comprehensive information is available on hypotension rates among hospitalized SARS-CoV-2 patients; it is thus premature to estimate what percentage of SARS patients of the currently ongoing epidemic can be safely treated with AT1R blockers without risking exacerbated hypotension.

The tentative suggestion to apply AT1R antagonists such as losartan and telmisartan as SARS-CoV-2 therapeutics for treating patients prior to the development of acute respiratory syndrome remains unproven until tried. At time of writing this brief commentary, the end of the COVID-19 epidemic is not in sight and drastic actions

are required (and being done) for containing its spread and death toll. Hence, the most rapid approach for assessing its feasibility is to analyze clinical patient records and apply datamining technologies to determine whether patients who were prescribed with AT1R antagonists prior to their diagnosis (for treating their hypertension, diabetic kidney disease, or other indications) had better disease outcome. Moreover, the percentage of people chronically medicated with AT1R blockers in the general population should be compared with the percentage among hospital admissions of SARS-CoV-2 infected patients presenting serious symptoms. If the latter percentage would be found to be significantly smaller, this would support the notion that AT1R antagonists confer protection from severe symptoms among SARS-CoV-2 infected individuals. Knowledge gained from such datamining of clinical records seems crucial for reducing the mortality and morbidity of SARS-CoV-2. At the same time, efforts must be made for developing a SARS-CoV-2 vaccine.

CONFLICT OF INTEREST

The author declares no potential conflict of interest.

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