Clinics in Surgery

Editorial
Published: 28 Jul, 2020

Losartan (AT1R Blockers): Beneficial Effects on COVID-19 Patients

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Editorial

The novel Coronavirus 2019 (COVID-19), officially known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of COVID-19, emerged in Wuhan, Hubei province, China. According to the World Health Organization, it has swept whole countries with a great rate of mortality, tremendous infection rate over 10 million people on the worldwide. COVID-19 has resulted in more fatalities than SARS-CoV as a binding to the Angiotensin-Converting Enzyme 2 (ACE2) and Middle East Respiratory Syndrome-related Coronavirus (MERS-CoV) as a binding to dipeptidyl peptidase-4 (CD26) epidemics combined [1] and severe threat to worldwide public health. ACE2 receptors are found in most organs, attached to the membrane of epithelial cells and/or smooth muscle cells. They are also present in epithelial cells in the upper and lower airway, and the major target cells of COVID-19 are type II pneumocytes, which produce lung-lubricating proteins for major lung function in the alveoli of the lower airway. The higher expression of ACE2 might also lead to a higher risk of SARS-CoV infection, and several studies have shown that ACEIs/ARBs could upregulate ACE2 expression [12]. Evidence has shown that the activation of the Renin–Angiotensin System (RAS) and the downregulation of ACE2 expression are involved in the pathological process of lung injury following SARS-CoV infection [3].

Recently, the elevated serum level of angiotensin II was highly detected in COVID-19 patients, and it showed a linear positive correlation to viral load and lung injury [4]. Angiotensin II (AT2), the vasoactive peptide, elicits vasoconstriction and releases aldosterone which causes sodium and water retention and vascular permeability. Thus, the intake of ACEIs/ARBs could probably relieve lung injury and absolutely decrease heart and renal damages resulting from RAS activation. ARBs are one of the potential candidates for medicating pulmonary damages by blocking the AT1R. A recent hypothesis suggested that AT1R inhibitors might be beneficial for patients infected by COVID-19 who exhibit pneumonia [5]. In addition, the British Medical Journal posted similar suggestions that the treatment of AT1R blockers to COVID-19 patients may bring positive therapeutic outcomes in a "rapid online response" on February 4th, 2020 [6]. The AT1R antagonists, losartan and olmesartan, are applied to reduce blood pressure in hypertensive patients, and as a result, expression levels or cardiac ACE2 increased about three-fold following 28 days of chronic treatment after myocardial infarction induced by coronary artery ligation of rats [7]. Losartan was also known to upregulate renal ACE2 expression in chronically treated rats [8]. In this regard, increased expression levels of urinary ACE2 were observed in hypertensive patients treated with the AT1R antagonist, olmesartan [9]. Therefore, medicating SARS-CoV-infected patients with AT1R blockers could enhance the expression of ACE2 and may strongly protect them from acute lung injuries due to better niche condition. Kuba confirmed that in SARS-CoV-infected mice, the expression of pulmonary ACE2 was downregulated accompanied by an increased vascular permeability and edema. They also mentioned that SARS-CoV spike protein alone could decrease the expression of pulmonary ACE2 and cause lung injury, which can be alleviated by ACEIs/ARBs. Until now, there is no experimental or clinical data showing the efficacy of ACEi/ARBs in COVID-19 patients, more generally, to patients suffering cardiovascular and renal diseases because the mortality is 12 times higher for SARS-CoV [10]. In terms of microenvironment, for niche therapy, it would be better to understand therapeutic microenvironments to block anti-inflammatory action which might be associated with cytokine storm, indicative of severity of SAR-CoV-2 [11]. From another aspect of aggressive diseases, some people's immune systems go into overdrive and launch a cytokine storm, which is caused by overreacted tissue damage, and subsequently kill people.

Mice treated with losartan following acid aspiration-induced acute lung injury and pulmonary edema compared with mice treated with placebo and recombinant human ACE2 infusions or losartan both prevented severe lung injury and pulmonary edema in ACE2-konckout mice and

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Received Date: *01 Jul 2020*
Accepted Date: *24 Jul 2020*
Published Date: *28 Jul 2020*

Citation:
Park SY, Chung M-J, Son J-Y, Lee E-J, Jeong K-S. Losartan (AT1R Blockers): Beneficial Effects on COVID-19 Patients. Clin Surg. 2020; 5: 2880.

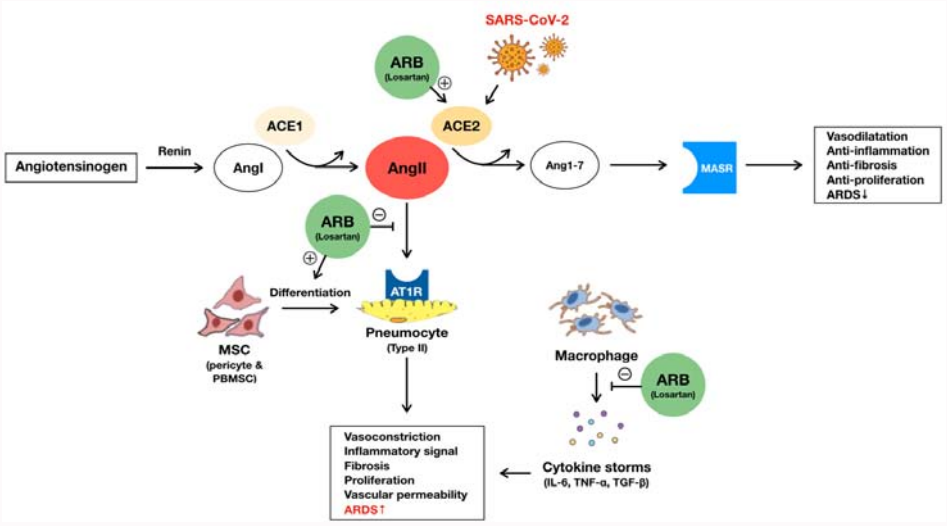

Figure 1: Better Niche Therapy for SARS-CoV-29 (COVID-19)-induced Lung Injury, Losartan, which serves as ARB, prevents ARDS growth by suppressing AngII pathway toward AT1R (angiotensin type 1 receptor blocker). The coronavirus is attached to ACE2 and blocks ACE2 pathway which leads to the transformation of AngII into Ang1-7 and Mas Receptor (MASR) to reduce Acute Respiratory Diseases Syndrome (ARDS). However, losartan activates ACE2, therefore increasing Ang1-7 which then attaches to MASR. Furthermore, losartan promotes the differentiation of mesenchymal stem cells, like adipose-derived stem cell, bone marrow-derived mesenchymal stem cell, peripheral blood mononuclear cells, especially pulmonary vascular pericyte which are enriched in pulmonary capillary bed, into the pneumocyte II and I and also it makes better niche compartment of pulmonary injuries by COVID-19 or secondary bacterial infection. Losartan also inhibits cytokine storms such as IL-6, TGF-β1 and other cytokines from macrophages that occur in this pathway. (+): Promote, (-): Blockade.

sepsis models of ARDS [12]. The interaction of tissue-specific stem cells with their particular microenvironment, known as the stem cell niche, is critical for the maintenance and regeneration of their COVID-19-induced damaged host tissues. Recent studies have shown that stem cell niches may be more important regulators of the qualities of stem cells than are stem cells themselves. To determine the mechanisms by which ARB promotes the differentiation of adipose derived stem cells, pericyte or other mesenchymal stem cells and/or satellite cells into myogenic cells, co-culture was performed with EGFP-positive ASCs derived from stromal vascular fractions and satellite cells *in vitro* following ARBs treatment, and this dramatically improved ASCs niche by inhibiting TGF- β1 in muscle injuries, leading to the promotion of muscle regeneration and inhibition of muscle fibrosis as well as enhanced number of myotube formation *in vitro* co-cultures. Moreover, musculoskeletal injuries could be improved by losartan, inducing better niche [13]. Mesenchymal stem cells are multipotent cells which found on immune effects and differentiation capacity *via* both paracrine manner and direct interaction with target cells during the process of body organ injuries. ARB treatment further enhanced the myotube formation in co-culture system of ASCs and satellite cells and increased the activation of satellite cells *via* activating Notch1 signaling through inhibiting TGF-β1 signaling, which leads to an increase in self-renewal of satellite cells, thereby enhancing myogenesis. In mature muscles, there are resident stem cells called satellite cells. Since they give rise to their own progeny and differentiated skeletal muscle cells, they play a key role in muscle regeneration. TGF-β1 negatively affects skeletal muscle regeneration by hampering satellite cell proliferation, and a systemically elevated TGF-β1 can cause hepatic inflammation, such as IL-6, which leads to fibrosis [14]. Furthermore, ARBs can show skeletal muscle, cardiac muscle, and diaphragmatic muscles at MDX mice [15] based on serologic and histopathologic profiles in the long-term administration of animal models and also have beneficial effects in combination therapy with exon skipping plus Losartan [16], and mouse adipose-derived stem cells and ARBS ameliorated muscle fibrosis and improved muscle regeneration in MDX mice [17]. Acute injury to healthy muscles or circulatory organs, such as the lung, heart, and diaphragm, has rapid and controlled inflammation that removes dead and injured cells and promotes replacement of injured tissues through mesenchymal stem cells to make a better niche compartment. Aged peoples loss more muscle mass and function, which contributes to disability and mortality, causing prolonged hospitalization and rehabilitation under pathologic condition which increased TGF-β signaling pathway to impaired muscle progenitors function and muscle repair; therefore, antagonism of TGF-β by losartan had beneficial impact on muscle remodeling of sarcopenic mice [18]. Nonetheless, losartan might have clinical benefits to the remodeling of COVID-19-injured lung tissues due to blockades of both AngII and TGF-β, especially in underlying diseases of people. Taking consideration suggests that it may rapidly regenerate on lung tissues, such as type II pneumocyte and other parenchymal lung tissues from pulmonary adjacent pericytes enrich in injured lung by coronavirus or secondary bacterial infections. To save patients struggling with COVID-19, the discovery of the life-saving drugs is desperately needed, and this hypothesis might provide treatment solution Figure 1.

Keywords: Losartan, Angiotensin-Converting Enzyme 2 (ACE2); Angiotensin II Type 1 Receptor (AT1R) blockers; COVID-19 epidemic; SARS-CoV-2; Transforming growth factor; Mesenchymal stem cells; Pricyte

Acknowledgement

This research was supported by the following grants: The National Research Foundation of Korea [NRF-2017R1EA1A1A01072781].

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