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Review Article

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers in an outbreak of SARS-CoV-2

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In COCID-19, hypertension, diabetes mellitus, coronary artery disease, and immunosuppression are comorbid conditions most often associated with poor prognosis. Angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers are widely used in the treatment of these diseases. Therefore, scientists turned their attention to these drugs and brought up the question of whether angiotensin converting enzyme inhibitors and angiotensin receptor blockers may be drugs that adversely affect prognosis in SARS-CoV-2 infection. The authors generally discussed the role of these drugs in SARS-CoV-2 infection through the same mechanisms. We also investigated the effects of these drugs on the immune system.

Currently, there is no definitive treatment method or vaccine available for COVID-19, which is rapidly spreading worldwide. Recently published data of patients are similar to each other. Especially advanced age is associated with poor prognosis. Hypertension, diabetes mellitus, coronary artery disease and immunosuppression are comorbid conditions which are most commonly associated with poor prognosis. Angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB) are widely used in the treatment of these diseases. Interestingly, those with chronic lung disease come after patients with above mentioned conditions [1-7]. Therefore, scientists turned their attention to these drugs and brought up the question of whether ACEIs and ARBs may be drugs that adversely affect prognosis in SARS-CoV-2 infection.

ACEIs and ARBs increase the expression of angiotensin converting enzyme 2 (ACE2) [8,9]. SARS-CoV-2 has four main structural proteins, one of which is the spike (S) protein that binds to the angiotensin converting enzyme 2 (ACE2) receptor and mediates subsequent fusion between the envelope and host cell membranes to aid viral entry into the host cell [10,11]. SARS-CoV-2 attaches to ACE2 receptors through the spike protein and invades tissues [12]. Based on this mechanism, some authors have argued that ACEI and/or ARB should not be used as they would enhance SARS-CoV-2 invasion, or some authors have reported their hesitation about the use of these drugs [1,6,13,14]. However, the fact that lung ACE2 expression is higher in young people, ACE2 expression decreases with age, and this decrease is more pronounced in men [15], do not support the hypotheses of these authors. This is because data on COVID-19 show that mortality rates are almost 0% in children and lower in women compared to men [2].

ACE2 is an important modulator of the renin-angiotensin system (RAS), which lowers Angiotensin II (Ang II) levels and increases production of Angiotensin 1-7 [Ang [1-7,16]. ACE inhibitors and ARBs exhibit lung-protective effects through providing ACE2-mediated increase in Ang [1-7]. Due to this mechanism, some authors have argued that ACEIs and ARBs would be beneficial or at least not be harmful in SARS-CoV-2 pneumonia. These authors have also argued that the virus reduced ACE2 levels after binding to ACE2, thereby inhibiting the protective effect of ACE2 in the lungs [17-20]. However, studies have shown that hypertensive patients who are hospitalized due to COVID-19 have a high rate of mortality [2,6]. This does not support the idea that ACEIs/ARBs protect the lungs by ACE2 upregulation.

Consequently, although both the hypothesis of authors who find ACEIs/ARBs harmful on the grounds that they enhance

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the virus invasion by ACE2 upregulation, and of authors who argue that ACEIs/ARBs protect patients from pneumonia on the grounds that they would increase production of Ang [1-7], by ACE2 upregulation are rational, neither hypothesis is supported by actual patient data. Therefore, we thought it was necessary to view ACEIs and ARBs from a wider framework.

One of the most interesting features of angioconverting enzyme (ACE) is its role in the immune response in addition to its role of regulating blood pressure [21]. Immune responses dependent on CD4+ T lymphocyte are critically important for mediating autoimmune diseases and controlling pathogen infection. MHC class II antigen processing pathway produces the cell surface MHC class II peptide complexes required for CD4+ T cell responses. Antibody production by B cells requires the aid of CD4 + T cells [22]. Major histocompatibility complex (MHC) molecules are cell surface molecules that present antigens to T cells and activate them and determine the direction of the T cell mediated immune response [23]. The newly synthesized MHC class II molecules combine with the invariant chain (Ii) in the endoplasmic reticulum [24]. Angiotensin converting enzyme (ACE) is a carboxyl peptidase [25], that is expressed by antigen-presenting cells (APC). ACE is a type I ectoenzyme associated with the cell membrane, but functionally active ACE is also found in the endoplasmic reticulum where ACE is involved in MHC class I antigen processing [26,27]. ACE is expressed with many different tissues, including APCs [28-30]. Zhao T, et al. showed in their study that ACE has a physiological role in the processing of peptides for MHC class II presentation via analysis of ACE null (knockout), normal type and ACE overexpressing (ACE10) mice and antigenpresenting cells derived from these mice. They demonstrated that the effectiveness of presenting MHC class II epitopes from ovalbumin and chicken egg lysosome was significantly affected by cellular ACE levels and that mice overexpressing ACE in myeloid cells had a much stronger CD4+ T cell and antibody response when immunized with ovalbumin. In the same study, mice overexpressing ACE were exposed to an ACE inhibitor, lisinopril and it has been observed that their previous capability to produce antibodies was completely eliminated [31]. Both in vitro and in vivo studies have consistently shown that ACE affects the peripheral activation of CD4+ T cells by APCs [32,33]. Harmer D, et al. have showed in their study that ACE expression was upregulated when APCs were stimulated by IFN-y or Listeria monocytogenes [27]. Khan Z, et al. have found in mouse experiments that overexpression of ACE in monocytes and macrophages regulates the immune responses of these cells and have shown that ACE inhibitors are detrimental to neutrophil function. However, they have demonstrated that ACEIs significantly reduced the bactericidal capacity of neutrophils after at least 7 days of use, rather than acute administration. They have also emphasized that individuals using ACEI may be susceptible to infections [34]. In another study, a higher incidence of urinary tract infections has been found in individuals taking ACE inhibitors [35].

Based on these mechanisms, we can easily say that ACEIs or ARBs disrupt the mechanism of antibody production in SARS-CoV-2 infection and contribute to the continuation of virus replication. We argue that the use of ACEIs/ARBs in patients with already impaired CD4/CD8 ratio due to aging may cause SARS-CoV-2 infection to be more fatal in these patients.

The immune system has been confirmed to play a vital role in the defense against SARS-CoV and MERS infections. In the acute phase of SARS-CoV infection, rapid reduction of lymphocytes in the peripheral blood has been observed, mainly T lymphocytes, and both CD4+ and CD8+ T lymphocytes. Lymphocyte loss occurred before abnormal changes appeared on the chest radiography [36-41]. In a study, it has been shown that T cell response before and during influenza infection and influenza-specific CD4+ T cells are associated with disease protection against influenza threat in humans [42]. Lymphocytes are also significantly decreased in severe type COVID -19 patients [43]. In our clinical observations, we found that severely ill patients had severe lymphopenia..

A low or inverted CD4/CD8 ratio is an immune risk phenotype and is associated with altered immune function, immune aging, and chronic inflammation in populations both infected and not infected with Human Immunodeficiency Virus-1 (HIV-1) [44]. The features of age-related inflammation are very similar to the inflammatory changes that occur during HIV-1 infection [45]. The prevalence of an inverted CD4/CD8 ratio increases with age. Inverse proportion is observed in 8% of the age group of 20-59 years, and in 16% of the age group of 60-94 years. Women of all age groups are less likely to have an inverse proportion than men [46]. Mouse models also emphasize the importance of age and estrogen on the CD4/CD8 ratio, because lower rates have been reported in mice after both natural menopause and ovariectomy [47]. This information gives us an explanation of why older patients compared to younger patients and men compared to women have higher mortality rates when infected with SARS-CoV-2.

Under lymphopenic conditions, T cells divide to maintain peripheral pool sizes. Deep chronic lymphopenia, characterized by poor T cell recovery in some HIV-1 infected patients, can cause intense homeostatic proliferation and T cell depletion and/or aging [48,49]. Homeostatic proliferation rates of the patients who were unable torecover CD4+ T cell countand have undetectable viral load (<50 copies/ml) among HIV-infected lymphopenic patients were higher than those of the patients using effective highly active antiretroviral therapy (HAART) who were able to recover CD+ 4 T cells [50]. In a cross-sectional study on 334 HIV-infected patients, a lower CD4/CD8 ratio during treatment has been shown to predict residual HIV viremia (≥1 copy / ml) detected by single copy assay [51].

Determining the CD4/CD8 ratio in COVID-19 may be important both for the treatment plan (such as the decision to treat with immune plasma as well as initiation and continuation of antiviral therapy), and for the estimation of viral load in recovered patients (including immune plasma donors). It may also be recommended that patients who have recovered from SARS-CoV-2 infection but have low CD4/CD8 ratio be followed up for undetectable viral load and risk of reactivation in the future, and also be considered for active immunization if a vaccine is found. In this context, COVID-19

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patients using ACEI and/or ARB may need to be monitored further for undetectable viremia after they have recovered. While following these patients, virtual reality system can be used to prevent transmission to healthcare professionals [52].

In summary, we believe that ACEIs and ARBs contribute to poor prognosis in patients with SARS-CoV-2 infection. However, it is necessary to quickly prove or refute this with actual patient data. We suggest that scientists should review the drugs used by patients who died or are negatively affected and determine the effect of those drugs on prognosis by comparative studies in countries where COVID-19 infection is widespread, and drugs that are actually found to be responsible should be urgently replaced with alternative drugs

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