BIOENGINEERING

**Angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor use and COVID-19-related outcomes among US Veterans**

Derington et al. sought to examine the effects of angiotensin II receptor blocker (ARB), and angiotensin-converting enzyme inhibitor (ACEI) use on US Veterans with treated hypertension and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In a retrospective cohort study, the experimenters analyzed data from the Veterans Health Administration (VHA) to derive separate outpatient and inpatient cohorts. The study was conducted on US veterans who tested positive between January 19, 2020, and October 15, 2020, met one-year continuous enrollment criteria and treated hypertension as ≥1 inpatient or ≥2 outpatient encounters. Furthermore, two exposure groups were compared: users of any ARB and/or ACEI vs. non-users of any ARB and/or ACEI, and users of an ARB vs. users of an ACEI. First, researchers determined that, for both inpatients and outpatients, current use of an ARB/ACEI was associated with a lower relative risk of COVID-19 related outcomes (all-cause mortality, ICU admission, dialysis, and/or mechanical ventilation). When evaluating ARB vs. ACEI, the group found no evidence of a significant association between ARB vs. ACEI users for hospitalization or mortality for the inpatient cohort but found a relatively lower risk in outpatient ARB users vs. ACEI users. The outcomes of this study reinforce the results of other small, randomized trials that also reported no increased risk of harm with ARB and/or ACEI usage for adults hospitalized for COVID-19. Tentatively, such findings provide reassurance of the continued use of ARBs and/or ACEIs among patients with an ongoing SARS-CoV-2 infection.

**Investigation of potential inhibitor properties of ethanolic propolis extracts against ACE-II receptors for COVID-19 treatment by molecular docking study.**

The study's objective was to investigate the potential of propolis extracts to bind to Angiotensin-Converting Enzyme (ACE) receptors and subsequently compare their performance to traditionally used ACE inhibitors. Propolis is a natural mixture generated by honey bees that is most commonly used when dissolved in 60-80% ethanol. Previous studies have demonstrated that flavonoids, an active ingredient in propolis, have a high inhibition potential for ACE. In addition, subsequent studies have identified ACE-II as a functional receptor for SARS-CoV-2, the virus that causes COVID-19, and the SARS-CoV-2 spike proteins have been found to have a strong binding affinity towards ACE-II. It is ACE-II that binds to SARS-CoV-2 and enables it to enter the host cell. In the study, flavonoids within the propolis were identified and used as a ligand in a molecular docking simulation with ACE-II. Through HPLC–UV chromatogram testing, ethanolic propolis was found to be rich in flavonoids, although composition varied with environmental and chemical conditions. Following the molecular docking simulation, the binding affinities of the flavonoids were evaluated by determining the binding energies and Kᵢ values. This analysis indicated that several phenolic compounds, most prominently rutin, are competitive inhibitors of ACE-II. Thus, the study concluded that ethanolic propolis may be used as a competitive inhibitor for ACE-II and may potentially be a natural protective agent against COVID-19. It is predicted that ACE-II inhibition via ethanolic propolis may have the potential to prevent or delay the
entry of COVID-19 into the cell due to the presence of flavonoids such as rutin. However, further in vivo and clinical trials are still needed to prove efficiency and safety before clinical use.

**Relationship between angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and COVID-19 incidence or severe disease**

This paper studied the relationship between ACE inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) and COVID-19 positivity and severe disease and found that the use of ACEIs and ARBs were significant predictors of COVID-19 positivity and severe disease outcomes. ACEIs and ARBs are commonly used to treat cardiovascular conditions and have been shown in previous studies to worsen COVID-19 disease outcomes and mortality. Some speculate that ACEIs and ARBs may have negative impacts on COVID-19 patients. The authors explored this by conducting a retrospective study on Hong Kong patients who underwent COVID-19 RT-PCR over seven months. Statistical analysis was used to determine how variables such as underlying conditions and medications, including ACEIs and ARBs, affected COVID-19 positivity rate and disease severity. ACEI and ARB use were higher among COVID-19 positive patients than controls. After correcting for confounding variables, the authors found a significant relationship between ACEI and ARB use and COVID-19 positivity and severe disease outcomes. This could be due to ACEIs and ARBs altering the expression of the SARS-CoV-2 entry receptor, ACE2. ACEIs and ARBs were found to have the same impact on positivity rates and disease severity. The results of this study vary from some other studies, which have found no clear relationship between ACEI/ARB use and COVID-19 positivity and severity.

**The role of IL-6 receptor inhibitor treatment in critical patient monitoring with COVID-19**

Çiylıtepe et al. highlighted the blood serum effects of Interleukin-6 (IL-6) receptor antagonist tocilizumab (TCZ), an immunosuppressive drug that has improved COVID-19 outcomes in some patients. In this study, TCZ was administered at 8mg/kg by two consecutive intravenous infusions 12 hours apart. 23 patients admitted to ICU for COVID-19 underwent this treatment and were monitored for 28 days. TCZ’s effects on blood serum levels of IL-6, lactate dehydrogenase (LDH), D-dimer, and ferritin, were then measured on the first and fifth day of treatment. Overall, decreased levels of CRP and ferritin and increased levels of D-dimer and IL-6 were observed. The increase in IL-6, despite the association with increased COVID-19 severity, can be explained by an inhibition of IL-6R mediated clearance due to TCZ binding to IL-6. Because levels of acute-phase reactants such as CRP, PCT, and ferritin decreased, this data could support the effectiveness of TCZ treatment due to a previously determined association between elevated ferritin levels and poor prognosis. Limitations of this study include retrospective design and a small sample size.
CLINICAL PRESENTATION AND MANAGEMENT

Delayed production of neutralizing antibodies correlates with fatal COVID-19

A quantitative longitudinal study among COVID-19 patients based on the differences in the kinetics of humoral responses of neutralizing antibodies and its correlation with fatal COVID-19 was conducted by Yale-New Haven Hospital between March 18, 2020 and May 27, 2020. 185 participants were hospitalized patients, 44 were non-hospitalized, 16 were vaccinated volunteers, and 105 were health care workers who served as uninfected controls for the study. COVID-19 disease severity was scored through review of electronic health records, and a total of 300 plasma samples were collected and ran through both ELISA and neutralization assays in order to assess antibody profiles. The study found a correlation between anti-spike (s) immunoglobulin G (IgG) levels, length of hospitalization, and increased disease severity. This correlation was time dependent, as deceased patients showed slower antibody dynamics compared to discharged patients, even though higher levels were reached later in the disease trajectory. Neutralizing antibody responses developed within 14 days of symptom onset correlated with recovery and improved disease trajectory and those induced later have shown to lose this protective effect. This data suggests that the loss of the protective role of antibodies in fatal COVID-19 is due to their late onset, and antibody-based therapies would be most beneficial within the first two weeks of disease.

Post-Acute Effects Of Sars-Cov-2 Infection In Individuals Not Requiring Hospital Admission: A Danish Population-Based Cohort Study

This study aimed to explore the post-acute impact on non-hospitalized Danish patients 2-6 months after being infected with SARS-CoV-2 by looking into incident drug use, overall healthcare, and hospital diagnoses. Eligible participants were those with a negative or positive RT-PCR test from February 27-May 31, 2020 in Denmark. Results show that 85.6% (8983) of the 10,498 eligible participants who tested positive were alive and not admitted to the hospital 2 weeks after their test while 1,310 participants were admitted two weeks after their test. 30.7% (2757) of the 8983 participants began new drug treatments compared to the 35.3% of participants who tested negative. Participants who tested positive (1.8%) were more likely to take bronchodilation drugs than those who tested negative (1.5%). After comparing positive vs negative participants, researchers found no increased risk of severe acute complications; however, the increased visit for COVID-19 positive patients to their primary-care physicians, may indicate the management of long-covid symptoms.

MODELS

Comparison of infection control strategies to reduce COVID-19 outbreaks in homeless shelters in the United States: a simulation study

This study assessed different infection control strategies to slow the spread of COVID-19 among people experiencing homelessness who reside in shelters using a microsimulation model. Health outcomes associated with each strategy were compared using polymerase chain reaction (PCR) survey data from COVID-19 outbreaks in five US homeless shelters across three cities from March 28 to April 10, 2020. The study found that combined strategies such as daily symptom screening, routine PCR testing, and universal masking helped reduce outbreak risk in scenarios with low reproduction numbers and low community incidence. However, outbreak risk increased with increasing community incidence and
transmission rate, and no combination of infection control strategies was found likely to prevent outbreaks in shelters with high transmission rates that were unable to maintain basic infection control practices (e.g., social distancing, reduced living density), as well as in cities with high community incidence. These findings suggest that while combining different infection control strategies may help reduce risk, it is necessary to provide non-congregate housing for people experiencing homelessness to prevent COVID-19 outbreaks.

NON-CLINICAL TRENDS

Assessing Child Abuse Hotline Inquiries in the Wake of COVID-19: Answering the Call

This cross-sectional study assessed the change in number of calls and texts to Childhelp, a national 24-hour multilingual and anonymous child abuse hotline, during the COVID-19 pandemic. Data from March-May 2020 was compared with that of the same period in 2019. Across both study periods, a total of 35,480 call and text inquiries were received. Overall, 96% of callers were adults, while most texters were younger than 18 years. During the pandemic, there was an increase in calls from neighbors, landlords and relatives, and a decrease in calls from school reporters and non-school-based mandated reporters, compared to 2019. Inquiries initially declined following school closures, possibly due to lack of exposure to mandated reporters. However, over time, both calls (mainly from parents) and texts increased. Overall, there was a 14% increase in the total number of inquiries in 2020 compared with 2019, possibly reflecting an increased rate of child maltreatment.

PHARMACEUTICAL INTERVENTIONS

Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients

The goal of this study was to explore the antibody response in individuals with solid organ transplants after their second SARS-CoV-2 vaccine dose in the United States. Eligible participants were those who completed the 2-dose mRNA vaccine and had no previous polymerase chain reaction-confirmed COVID-19. Results show that of the 658 participants, 98 (15%) participants had an antibody response after 1 dose and after two doses, 357 had a response (54%). After receiving the first dose, 259 (39%) had no response, but once they received the second dose, they had a successful response. Although the humoral response increased after 2 doses, solid organ transplant recipients remain vulnerable to COVID-19 and additional research is needed to improve vaccine response for this population.

Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant

The authors sought to evaluate the efficacy of the NVX-CoV2373 nanoparticle COVID-19 vaccine (Novavax vaccine) in response to the emergence of the B.1.351 SARS-CoV-2 variant. 4387 participants from South Africa were enrolled from August 17, 2020 through November 25, 2020. The participants were either healthy adults from the ages of 18 to 84
years who were HIV-negative (2684 participants), or they were HIV-positive with a medically stable condition. Participants were randomly assigned to receive either the NVX-CoV2373 vaccine or a placebo injection. Of the 4387 participants who received injections, only 4332 received both injections. Among all patients who were seronegative at baseline, 44 cases of symptomatic (mild-to-moderate) COVID-19 were observed with 15 participants from the vaccine group and 29 from the placebo group, corresponding to a vaccine efficacy of 49.4%. Among the HIV negative participants who were seronegative at baseline, symptomatic COVID-19 was observed in 11 participants from the vaccine group and 27 participants from the placebo group, corresponding to a vaccine efficacy of 60.1%. 92.7% of the sequenced isolates were the B.1.351 variant and in a post hoc analysis; the vaccine efficacy against the variant was 51.0% among the HIV-negative participants and 43.0% in the entire participant sample. These findings suggest high NVX-CoV2373 vaccine efficacy against the B.1.351 variant.

**Tocilizumab in patients admitted to the hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label platform trial**

Researchers studied the drug Tocilizumab in a randomized controlled trial to help treat hypoxia and inflammation in hospitalized adult COVID-19 patients. A total of 2,022 cases received a single dose of tocilizumab based on their bodyweight over 60 minutes, and 2,094 controls received usual care. Tocilizumab use was correlated with reduced mortality and greater probability of discharge from hospital in 28 days compared with usual care alone. Additionally, the drug was correlated with reduced risk of requiring invasive mechanical ventilation or death in those not already on ventilation compared to usual care alone. These results show that for patients with severe COVID-19, treatment with tocilizumab can increase survival, discharge, and reduce ventilation.

**TRANSMISSION PATTERNS**

**Prevalence of SARS-CoV-2 in urban and rural Ethiopia: Randomized household serosurveys reveal level of spread during the first wave of the pandemic**

Researchers evaluated seroprevalence of SARS-CoV-2 antibodies in Ethiopia using the COVID-19 IgM/IgG rapid test. In the capital city of Addis Ababa, 956 households were tested, and in rural Jimma region, 900 were tested. Results showed that between 22 July and 10 August, Addis Ababa had a 1.9% prevalence of IgG, and a combined IgM/IgG prevalence of 3.5%. Between 19 August and 2 September, Jimma had a prevalence of IgG at 0.5% and IgM/IgG at 1.6%. In Addis Ababa, prevalence was slightly higher for men and lower in the 18-34 age group, whereas in Jimma no difference was detected in those categories. These data show more COVID-19 disease in the capital city than in rural areas and demonstrate a slower spread of SARS-CoV-2 in Ethiopia in comparison to other countries in Europe and America.
ADDITIONAL RESOURCES
UCSF Library COVID-19 Research and Information Resources
UCSF Institute for Global Health Sciences COVID-19 Resources
UC Davis One Health Institute COVID-19 FAQs
Harvard Viswanath Lab Myths vs Facts

Note on this Document: This document was assembled by graduate and doctoral students attending the University of California, San Francisco with the intent of facilitating the rapid dissemination of information to the global community in order to help during this time. Kaylie Bair, Amanda Chan, Sara Covin, Hannah Han, Deandräa Lee, Nicole Lin, Bryan Maghen, and Mica Reyna contributed to these summaries. This work is volunteer based.

References:


3. Tse, Garya; Zhou, Jiandong; Lee, Sharenc; Wong, Wing Takd; Li, Xintaoe; Liu, Tonga; Cao, Zhidongf; Zeng, Daniel Dajunf; Wai, Abraham K.C.g; Wong, Ian Chi Keih; Cheung, Bernard Man Yungi; Zhang, Qingpengb Relationship between angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and COVID-19 incidence or severe disease, Journal of Hypertension: April 09, 2021 - Volume Publish Ahead of Print - Issue - doi: 10.1097/HJH.0000000000002866


