**PICO Search Assignment Worksheet** **Name: Jay Kolasinac**

**Brief description of patient problem/setting (summarize the case very briefly)**

56M, with PMH of DMII, HTN, and CAD, presents with fever, body aches, and SOB to his PCP. Patient is discovered to be COVID-19 positive. Patient states he has heard of REGEN-COV and wonders if it could help prevent him from going to the hospital/dying.

**Search Question:** In patients diagnosed with COVID-19, is Casirivimab/Imdevimab (*REGEN-COV*) effective at reducing the risk of hospitalization/death?

**Question Type:** What kind of question is this? (boxes now checkable in Word)

| | | |
|---|---|---|
| ☐Prevalence | ☐Screening | ☐Diagnosis |
| ☒Prognosis | ☒Treatment | ☐Harms |

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?

**Please explain your choices.**

Since my topic is a relatively new topic, I will expect to find more observational studies as well as randomized clinical trials testing the drug question. Since it is still new and COVID is still here, I do not expect to find many systematic reviews or meta-analyses on the topic, but if I do, that will be a great plus and high levels of evidence. Retrospective studies would also be articles that I may include in my PICO to identify outcomes in patients who were previously given monoclonal antibodies.

**PICO search terms:**

| P | I | C | O |
|---|---|---|---|
| Adults | Casirivimab | Placebo | Reduced risk of hospitalization |
| Covid-19 | Imdevimab | None | Reduced risk of death |
| | Regen-COV | | Increase survival rate |
| | | | |

**Search tools and strategy used:**

| Database | Terms | Filter | # of Articles |
|---|---|---|---|
| PubMed | Casiriviamb imdevimab covid 19 | Medline, last 5 years | 62 |
| | Regen-cov covid 19 | Medline, last 5 years | 17 |
| ScienceDirect | Casiriviamb imdevimab covid 19 | Last 5 years | 0 |

| | | | |
|---|---|---|---|
| | Regen-cov covid 19 | Last 5 years | 31 |
| MEDLINE Complete | Casiriviamb imdevimab covid 19 | Last 5 years | 1 |
| | Regen-cov covid 19 | Last 5 years | 245 |

I found a good number of articles related to the monoclonal antibody treatment. It was important that I included the brand name of the drug in my search terms because the generic names, depending on the database, yielded very minimal results. Since COVID-19 and the use of new medications in the fight against the virus is still relatively brand new, I can expect a good number of results but not a plethora of articles. I narrowed down the results to be Medline and within the last 5 years.

**Results found:**

**Article 1**

**Citation:**

O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19 [published online ahead of print, 2021 Aug 4]. *N Engl J Med*. 2021;NEJMoa2109682. doi:10.1056/NEJMoa2109682

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8362593/

**Article Type:**

RCT

**Abstract:**

**BACKGROUND R**EGEN-COV (previously known as REGN-COV2), a combination of the monoclonal antibodies casirivimab and imdevimab, has been shown to markedly reduce the risk of hospitalization or death among high-risk persons with coronavirus disease 2019 (Covid-19). Whether subcutaneous REGEN-COV prevents severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and subsequent Covid-19 in persons at high risk for infection because of household exposure to a person with SARS-CoV-2 infection is unknown.

**METHODS** We randomly assigned, in a 1:1 ratio, participants (≥12 years of age) who were enrolled within 96 hours after a household contact received a diagnosis of SARSCoV-2 infection to receive a total dose of 1200 mg of REGEN-COV or matching placebo administered by means of subcutaneous injection. At the time of randomization, participants were stratified according to the results of the local diagnostic assay for SARS-CoV-2 and according to age. The primary efficacy end point was the development of symptomatic SARS-CoV-2 infection through day 28 in participants who did not have SARS-COV-2 infection (as measured by reverse-transcriptase– quantitative polymerase-chain-reaction assay) or previous immunity (seronegativity).

**RESULTS** Symptomatic SARS-CoV-2 infection developed in 11 of 753 participants in the REGEN-COV group (1.5%) and in 59 of 752 participants in the placebo group (7.8%) (relative risk reduction [1 minus the relative risk], 81.4%; P104 copies per milliliter) was shorter (0.4 weeks and 1.3 weeks, respectively). No dose-limiting toxic effects of REGEN-COV were noted.
**CONCLUSIONS** Subcutaneous REGEN-COV prevented symptomatic Covid-19 and asymptomatic SARS-CoV-2 infection in previously uninfected household contacts of infected persons. Among the participants who became infected, REGEN-COV reduced the duration of symptomatic disease and the duration of a high viral load. (Funded by Regeneron Pharmaceuticals and others; ClinicalTrials.gov number, NCT04452318.).

**Key points:**

- Patients randomly assigned in a 1:1 ratio
- Covid positive patients
- Either received 1200 mg of REGEN-COV or a placebo administered both subcutaneously
- The REGEN-COV group experienced fewer symptomatic developments from the virus a quicker resolution of symptom times 2 weeks shorter than the placebo group, and a shorter duration of high viral load
-

**Why I chose this article:**

- It was a RCT review
- It specifically focused on my PICO question.
- Published in within the last month
- Over 1,000 patients included in the study

**Article 2**

**Citation:**

Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. *N Engl J Med*. 2021;384(3):238-251. doi:10.1056/NEJMoa2035002

**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7781102/**

**Article Type:**

RCT

**Abstract**:

**BACKGROUND** Recent data suggest that complications and death from coronavirus disease 2019 (Covid-19) may be related to high viral loads.
**METHODS** In this ongoing, double-blind, phase 1–3 trial involving nonhospitalized patients with Covid-19, we investigated two fully human, neutralizing monoclonal antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein, used in a combined cocktail (REGN-COV2) to reduce the risk of the

emergence of treatment-resistant mutant virus. Patients were randomly assigned (1:1:1) to receive placebo, 2.4 g of REGN-COV2, or 8.0 g of REGN-COV2 and were prospectively characterized at baseline for endogenous immune response against SARS-CoV-2 (serum antibody–positive or serum antibody–negative). Key end points included the time-weighted average change in viral load from baseline (day 1) through day 7 and the percentage of patients with at least one Covid-19–related medically attended visit through day 29. Safety was assessed in all patients.

**RESULTS** Data from 275 patients are reported. The least-squares mean difference (combined REGN-COV2 dose groups vs. placebo group) in the time-weighted average change in viral load from day 1 through day 7 was −0.56 log10 copies per milliliter (95% confidence interval [CI], −1.02 to −0.11) among patients who were serum antibody– negative at baseline and −0.41 log10 copies per milliliter (95% CI, −0.71 to −0.10) in the overall trial population. In the overall trial population, 6% of the patients in the placebo group and 3% of the patients in the combined REGN-COV2 dose groups reported at least one medically attended visit; among patients who were serum antibody–negative at baseline, the corresponding percentages were 15% and 6% (difference, −9 percentage points; 95% CI, −29 to 11). The percentages of patients with hypersensitivity reactions, infusion-related reactions, and other adverse events were similar in the combined REGN-COV2 dose groups and the placebo group.

**CONCLUSIONS** In this interim analysis, the REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline. Safety outcomes were similar in the combined REGN-COV2 dose groups and the placebo group. (Funded by Regeneron Pharmaceuticals and the Biomedical and Advanced Research and Development Authority of the Department of Health and Human Services; ClinicalTrials.gov number, NCT04425629.)

**Key points:**

- Double blind RCT
- Non hospitalized patients
- Patients were given either REGEN-COV 2.4g, 8.0g or placebo
- End points: time-weight average change in viral load since day 1 to day 7
- Higher viral loads have been correlated with an increase risk of death and REGEN-COV reduced viral load
- 275 patients reported
- 6% of patients in the placebo group required a hospital visit
- Only 3% of the combined REGEN-COV groups required a hospital visit

**Why I chose this article:**

- It was a RCT
- It specifically focused on my PICO question.
- Published within the last year
- Compared different dosages of REGEN-COV

**Article 3**

**Citation:**

Ganesh R, Philpot LM, Bierle DM, et al. Real-World Clinical Outcomes of Bamlanivimab and Casirivimab-Imdevimab among High-Risk Patients with Mild to Moderate Coronavirus Disease 2019 [published online ahead of print, 2021 Jul 19]. *J Infect Dis.* 2021;jiab377. doi:10.1093/infdis/jiab377
**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8344643/**

**Article Type:**

Retrospective Cohort Study

**Abstract**:

**Background**

Bamlanivimab and casirivimab-imdevimab are authorized for treatment of high-risk patients with mild to moderate coronavirus disease-2019 (COVID-19). We compared the outcomes of patients who received these therapies to identify factors associated with hospitalization and other clinical outcomes.

**Methods**

Adult patients who received monoclonal antibody from November 19, 2020 to February 11, 2021 were selected and divided into those who received bamlanivimab (n=2747) and casirivimab-imdevimab (n=849). The 28-day all-cause and COVID-19-related hospitalizations were compared between the groups.

**Results**

The population included 3596 patients; median age was 62 years; and 50% were female. All had ≥1 medical comorbidity; 55% had multiple comorbidities. All cause- and COVID-19-related hospitalization rates at 28 days were 3.98% and 2.56%, respectively. After adjusting for medical comorbidities, there was no significant difference in all cause- and COVID-19-related hospitalization rates between bamlanivimab and casirivimab-imdevimab (adjusted HR, 1.4, 95% CI 0.9-2.2 and 1.6, 95% CI 0.8-2.7, respectively). Chronic kidney, respiratory and cardiovascular diseases, and immunocompromised status were associated with higher likelihood of hospitalization.

**Conclusion**

This observational study on the use of bamlanivimab and casirivimab-imdevimab in high-risk patients showed similarly low rates of hospitalization. The number and type of medical comorbidities are associated with hospitalizations after monoclonal antibody treatment.

**Key points:**

- Patients received monoclonal antibodies from November 19,2020 to February 11, 2021.
- One group received Bamlanivimab while the other received casirivimab-imdevimab
- On day 28, the all cause and COVID-19 related hospitalizations were compared between the two groups.
- Over 3500 patients included in the study
- Casirivimab-imdevimab group rates at day 28 for all-cause hospitalization was lower (2.83%) vs the bamlanivimab group (4.34%)

- After adjusting for medical comorbidities, they was no significant difference between the two groups regarding all-cause mortality

**Why I chose this article:**

- Published with the last 2 months, very recent
- Included over 3,500 patients
- Focused directly on my PICO question
- Compared the effects of another drug

**Article 4**

**Citation:**

R.R. Razonable et al., CasirivimabImdevimab treatment is associated with reduced rates of hospitalization among high-risk patients with mild to moderate coronavirus disease-19, EClinicalMedicine (2021), https://doi.org/10.1016/j.eclinm.2021.101102

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00382-5/fulltext

**Article type:**

Retrospective cohort study

**Abstract:**

**Background**: Real-world clinical data to support the use of casirivimabimdevimab for the treatment of out-patients with mild to moderate coronavirus disease-19 (COVID-19) is needed. This study aimed to assess the outcomes of casirivimabimdevimab treatment of mild to moderate COVID-19.

**Methods**: A retrospective cohort of 696 patients who received casirivimabimdevimab between December 4,2020 and April 9, 2021 was compared to a propensity-matched control of 696 untreated patients with mildto moderate COVID-19 at Mayo Clinic sites in Arizona, Florida, Minnesota, and Wisconsin. Primary outcome was rate of hospitalization at days 14, 21 and 28 after infusion.

**Findings**: The median age of the antibody-treated cohort was 63 years (interquartile range, 5271); 45¢5%were65 years old; 51.4% were female. High-risk characteristics were hypertension (52.4%), body mass index35 (31.0%), diabetes mellitus (24.6%), chronic lung disease (22.1%), chronic renal disease (11.4%),congestive heart failure (6.6%), and compromised immune function (6.7%). Compared to the propensity-matched untreated control, patients who received casirivimabimdevimab had significantly lower all-cause hospitalization rates at day 14 (1.3% vs 3.3%; **Absolute Difference**: 2.0%; 95% confidence interval (CI):0.53.7%), day 21 (1.3% vs 4.2%; Absolute Difference: 2.9%; 95% CI: 1.24.7%), and day 28 (1.6% vs 4.8%; Abso-lute Difference: 3.2%; 95% CI: 1.45.1%). Rates of intensive care unit admission and mortality at days 14, 21and 28 were similarly low for antibody-treated and untreated groups.

**Interpretation**: Among high-risk patients with mild to moderate COVID-19, casirivimabimdevimab treatment was associated with a significantly lower rate of hospitalization.

| |
|---|
| **Key points:**<br>- Retrospective study<br>- 696 patients received casirivimab-imdevimab between Dec. 4th 2020 and April 9, 2021<br>- Compared to control: those who received casirivimab-imdevimab had significantly lower all-cause hospitalization rates at day 14<br>- ICU and mortality rates at days 14, 21, and 28 were similarly low those treated with the antibodies and those non treated |
| **Why I chose this article:**<br>- The study ended a few months ago, very recent<br>- Focused directly on my PICO question<br>- Measured hospitalization rates, mortality, and ICU admission rates |

**What is the clinical "bottom line" derived from these articles in answer to your question?**

Casirivimab-imdevimab (*REGEN-COV*) is a drug combination regimen that is authorized for the treatment of COVID-19 to reduce the risk of hospitalization/death. The monoclonal antibody medications were quickly studied and tested on patients to demonstrate any effects in reducing hospitalization rates/death. All four of the articles included in this PICO included results that demonstrated *REGEN-COV* as an agent capable to reduce the rate of hospitalization or death in those patients who received the treatment. When compared to other monoclonal antibodies, such as bamlanivimab in article 3, there was no significant difference in hospitalization rates/death when adjusted for comorbidities, although, patients who were treated with REGEN-COV were seen to have a lower all-cause hospitalization compared to bamlanivimab at day 28. Is REGEN-COV the holy grail of monoclonal antibody to help anyone with comorbidities? Probably not. It is a drug that can be effective for patients with far fewer comorbidities and with mild-moderate disease states of the virus as evident in the articles above. Individuals with multiple comorbidities were seen to have higher hospitalization rates/deaths even with the monoclonal antibody treatment. I believe more research needs to be conducted to determine the exact patient demographic this can target, because not every patient has the same number of comorbidities. Once a clear cut patient population is known to benefit from the treatment, this can help decrease COVID-19 hospitalizations and make it easier for providers to recommend the monoclonal antibodies to their patients instead of sending each and every COVID-19 positive patient to receive the treatment where it may or may not work.