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Monoclonal Antibodies vs. Symptomatic Treatment of Hospitalized Patients with COVID-19

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by

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Abstract

The SARS-CoV-2 virus, or COVID-19, was the virus responsible for the worldwide pandemic declared in March, 2020. Individuals can experience a wide variety of symptoms ranging from fever, fatigue, cough, and, in more severe cases, hypoxia requiring invasive mechanical ventilation (IMV). Until recently, symptomatic care was the protocol for patients infected with COVID-19. The use of oxygen for mild hypoxia and antipyretics for fevers was considered the standard of care (SOC). The use of antiviral medications, such as monoclonal antibodies, has been proposed in the treatment of acute COVID-19 infection. The purpose of this literature review is to determine if monoclonal antibodies could be considered as treatment options for high risk patients hospitalized with COVID-19. A literature review was performed on PubMed using the following MESH terms: COVID-19, monoclonal antibodies, and hospitalization. Articles from 2020 to the present were included in the search. Studies were limited to randomized control trials and clinical trials. Out of 97 total search results, 20 articles were relevant to the search. 10 articles were removed due to the studies being performed as outpatient procedures. Two studies were removed as they were reviews. There are three common goals throughout the studies analyzed in this literature review regarding the use of monoclonal antibodies in patients with COVID-19. The first goal is to decrease the length of hospital admission, the second is to decrease the severity of symptoms, shown by a decrease in inflammatory markers, that may be lethal to more fragile patients, and the third is to reduce the overall mortality of COVID-19. The literature review showed monoclonal antibodies are beneficial when their mechanism of action causes direct inhibition of the inflammatory pathway.

Keywords: SARS-CoV-2, COVID-19, monoclonal antibodies, length of admission, inflammatory markers

Introduction

According to the Centers for Disease Control (CDC), The SARS-CoV-2 virus, or COVID-19, is responsible for 6,622,268 patient hospitalizations and 1,163,040 deaths as of December 23rd, 2023 (Centers for Disease Control, COVID Data Tracker). Patients can experience a wide variety of symptoms when infected with COVID-19, some more severe than others. These symptoms can range from cough, fatigue, fever, and, in more severe cases, hypoxia which can lead to mechanical ventilation. Patients with comorbidities such as diabetes, coronary artery disease, and chronic obstructive pulmonary disease were considered to be at higher risk for hospitalization and death with the highest risk population being patients 85 years or older. However, COVID-19 has been shown to affect all patients differently. As of December 16th, 2023, the World Health Organization (WHO) has identified 10 variants of the SARS-CoV-2 virus, with the Omicron variant having more than 30 subvariants. Research is ongoing to determine the different variants' ease of transmission and severity of symptoms caused by that variant. In December 2020, a vaccine for the SARS-CoV-2 virus was made available. Research on the efficacy of the vaccine for the various SARS-CoV-2 variants is still ongoing, but the WHO does believe patients who are vaccinated will experience more mild symptoms than patients who are unvaccinated.

COVID-19 was first discovered in Wuhan, China, in December of 2019. By March of 2020, COVID-19 was declared a pandemic. Typically transmitted through respiratory droplets, the COVID-19 pandemic strained healthcare systems in most countries leading to significant economic losses. COVID-19 has an average incubation period of 6.4 days, and most patients experience symptoms of fever, cough, fatigue, and dyspnea (Ochani et al.). As the disease progresses, patients are at increased risk of suffering from a “cytokine storm”.

Cytokines such as interleukins (ILs), interferons (IFNs), colony-stimulating factors (CSF), and tumor necrosis factors (TNFs), among many others, induce the inflammation cascade causing these cytokine storms. While the pathogenesis of a cytokine storm is not fully understood, it is known to be caused by various bacterial or viral infections, rheumatic conditions, sepsis, or drugs that cause an immune response. Pathogens invade the body starting the body's innate immunity first. Infected epithelial cells release IL-1B and IFN-a/B, which in turn stimulate the natural killer (NK) cells. IFN-y, activated by IFN-a/B activates macrophages and releases large amounts of cytokines TNF-a and IL-12, which then activate the NK cells (Zhang 2020). This creates positive feedback between the macrophages and NK cells significantly increasing cytokine levels. Cytokines both promote and restrict each other to control the proliferation and differentiation of cells and regulate the inflammatory and immune responses during disease processes (Zhang 2020). While management is mostly supportive, the use of anti-viral agents and various cytokine blockers has shown promising results in reducing the severity of symptoms.

Statement of the Problem

Until recently, symptomatic care was the protocol for patients infected with COVID-19. The use of oxygen for mild hypoxia and antipyretics for fevers was considered the standard of care (SOC). The use of antiviral medications, such as monoclonal antibodies, has been proposed in the treatment of acute COVID-19 infection. Many monoclonal antibodies are known inhibitors of cytokines, which are involved in the inflammatory process, whereas the current SOC focuses on treating the inflammation rather than the inflammation itself.

Research Question

In patients who have been hospitalized for COVID-19, will treatment with monoclonal antibodies decrease mortality risk as opposed to symptomatic care alone?

Methods

A literature review was performed on PubMed using the following MESH terms: COVID-19, monoclonal antibodies, and hospitalization. Articles from 2020 to the present were included in the search. Studies were limited to randomized control trials and clinical trials. Out of 97 total search results, 20 articles were relevant to the search. 10 articles were removed due to the studies being performed as outpatient procedures. Two studies were removed as they were reviews.

Literature Review

Safety and efficacy of Netakimab in the management of COVID-19

Avdeev et al. (2021) conducted a control study in August 2020 involving 171 patients hospitalized with COVID-19. The purpose of this study was to determine if the monoclonal antibody netakimab can be used as a safe and effective treatment for patients infected with COVID-19. Patients over the age of 18 years old, with a $SpO_2 \leq 92\%$, and bilateral pneumonia, who have one of the following criteria: a C-reactive protein (CRP) ≥40 mg/L, a fever ≥ 38 degrees Celsius for greater than three days, lymphocytes $\leq 0.8x10^9$/L, and leukocytes $\leq 3.0 \times 10^9$/L were selected for this study. Patients who were hospitalized in the intensive care unit, treated with a different cytokine inhibitor, or had signs of a bacterial infection were excluded from the study. Patients were divided into experimental and control groups. Patients in the control group were matched to patients in the experimental group by age, SpO_2/FiO_2 ratio, National Early Warning 2 (NEWS2) score, and CRP levels. The NEWS2 metric is based on physiological variables such as heart rate, blood pressure, respiratory rate, temperature, level of

consciousness, and oxygen saturation and is scored from 0-20. Patients in the control group received the standard of care therapy consisting of azithromycin, low-molecular-weight heparin, hydroxychloroquine, and corticosteroids. Patients in the experimental group received the standard of care therapy as well as a subcutaneous administration of 120 mg netakimab, an IL-17 antagonist monoclonal antibody.

The parameters were measured at day one, and again at day three. On day one the average baseline body temperature in the control group was 37.7 degrees Celsius, while the netakimab group had an average temperature of 37.5 degrees Celsius ($p = 0.18$). The baseline average SpO_2/FiO_2 ratio in the control group was 253. The netakimab group had an average ratio of 267 ($p = 0.32$). The average CRP level for the control group was 102 mg/L, with the netakimab group having a baseline average CRP level of 113 mg/L ($p = 0.1$). Significant outcomes were found in body temperature, SpO_2/FiO_2 ratio, NEWS2 score, and CRP levels. On day three, these parameters were measured again. On day three, the average body temperature for the control group was reduced to 36.9 degrees Celsius, while the netakimab group's average temperature was reduced to 36.7 degrees Celsius ($p = 0.01$). The day three average SpO_2/FiO_2 ratio had increased to 266 in the control group, and the netakimab group had an average ratio that had increased to 272 ($p = 0.03$). The most significant change was noted in the average CRP levels. The day three average CRP levels for the control group had decreased to 57mg/L, while the average of the netakimab group had decreased to 29 mg/L ($p < 0.001$). A significant decrease in the length of hospital admission was noted in the netakimab group (15 (11-19) vs 16 (14-20) days in the control group ($p = 0.02$) (Avdeev et. al, 2021).

All adverse events recorded were considered mild and did not show a statistical significance. A total of 55 patients had adverse events in the control group, whereas a total of 57

patients had adverse events in the netakimab group. Adverse events were described as weakness, blood pressure higher than 140/90 mmHg, AST three times the upper limits of normal (ULN), ALT three times the ULN, diarrhea, dyspepsia, nausea, dyspnea, elevated creatinine, headache, and rashes. Overall, the use of netakimab showed an improvement in oxygenation levels, body temperature, and a decrease in the CRP inflammatory marker (Avdeev et al., 2021).

One strength of this article was the criteria Avdeev et al. (2021) used to select eligible patients for this trial. By establishing these criteria, they hypothesized that these patients would show great similarity in the parameters they would use to assess the efficacy of netakimab. Another strength was the use of a controlled study on patients with similar baselines to evaluate the effectiveness of netakimab. One weakness of this study is that the authors did not go into detail about each patient's adverse effects they experienced from the infusions they received. Describing the adverse events as mild is subjective, and it is difficult to objectively base the severity on this metric.

In February 2020, Bryushkova et al. (2022) conducted an observational cohort study including 154 patients hospitalized with COVID-19. The purpose of this study was to determine if the monoclonal antibody netakimab could be used as an effective treatment for patients infected with COVID-19. Adult patients with SARS-CoV-2 infection confirmed by reverse transcriptase-polymerase chain reaction were eligible if they had symptoms of acute respiratory failure such as fever, cough, and muscle pain or radiologically-defined viral pneumonia confirmed by computed tomography. Bryushkova et al. used the NEWS2 metric. Patients were excluded from this study if their serum CRP level was higher than 140 mg/L on the starting therapy day, if they had a NEWS2 score that was unknown, or higher than 6, if they had

hematological, hepatic, or renal impairment, if there was no information on death or hospital discharge, or if there was evidence of concomitant bacterial infection.

Patients were divided into four groups. Thirty-eight patients were assigned to receive 4 mg of baricitinib either once or twice per day for a period of three to eight days. Baricitinib is a JAK1/2 inhibitor that is commonly used in the treatment of rheumatoid arthritis by decreasing the level of phosphorylated STAT proteins, thereby blocking IL-6, IL-12, IL-23, and IFN-y proinflammatory signals. Forty-eight patients assigned to the netakimab group received a single 120 mg subcutaneous injection. Thirty-four patients assigned to the tocilizumab group received a single 400 mg intravenous dose. Thirty-four patients were assigned to receive standard of care (SOC) that consisted of symptomatic treatment including fever relief, decongestants, or bronchodilators as needed.

The primary outcomes of this study were CRP (mg/L) and lactic dehydrogenase (LDH, U/L) inflammatory markers, absolute neutrophil count (ANC, $x10^9$/L), absolute lymphocyte count (ALC, $x10^9$/L), and the neutrophil-to-lymphocyte ratio (NLR). Secondary outcomes were the NEWS2 score, time from admission to discharge from the hospital, and mortality rate. All parameters were measured at baseline, day three, and day five (Bryushkova et al., 2022).

While all groups showed a decrease in the average CRP levels, tocilizumab and netakimab were the only treatments to show a significant decrease in average CRP levels from baseline. On day zero, the average CRP level in the tocilizumab group was 27.39 mg/L, which had decreased to 6.6 mg/L by day three and 2.64 mg/L by day five ($p= 0.00001$). The baseline average CRP level in the netakimab group was 17.34 mg/L, which had decreased to 7.89 mg/L by day three and 4.84 mg/L by day five ($p=0.0008$). The netakimab group was the only group to see a significant reduction in LDH. The average LDH in the netakimab group was 247.6 U/L on

day zero and had decreased to 210 U/L by day three (p=0.029). There was no significant difference in LDH from day three to day five.

Netakimab showed a significant difference in average ANC from day zero (3.05 $x10^9$/L) to day three (5.4 $x10^9$/L) and again on day five (6.2 $x10^9$/L) (p= 0.000069). Baricitinib was the only group to show a significant difference in average ALC from day zero (1.65 $x10^9$/L) to day three (2.65 $x10^9$/L) and again on day five (2.4 $x10^9$/L) (p= 0.03108). Both baricitinib and netakimab showed significant differences in the NLR. At baseline, the baricitinib group had an average NLR of 2.41, an average of 1.18 on day three, and an average of 1.36 on day five (p= 0.0000437). The netakimab group had an average NLR of 2.32 on day zero, an average of 5.26 on day three, and then showed a decrease to 5.13 on day five (p= 0.008684).

None of the groups showed any significant change in the NEWS2 score, length of hospital stay, or mortality. Approximately 90% of patients in each group were discharged from the hospital by day 14. One patient in the baricitinib group and three patients in the SOC group had died. No patient deaths were recorded in both the netakimab and tocilizumab groups.

One of the greatest strengths of this study was the use of different medications in each group. Bryushkova et al. were able to measure the same parameters over the entire cohort to evaluate the efficacy of each medication. One weakness of this study was that these patients were a small portion of a much larger group of patients from a previous trial where each patient received different medications and it is not stated which patient received what medication in the previous trial. Another weakness of this study is the authors did not describe how they divided the patients into each group.

Safety and efficacy of Lenzilumab in the management of COVID-19

Temesgen et al. (2023) conducted a randomized, blinded, controlled trial using the monoclonal antibody lenzilumab or a placebo in the treatment of hospitalized patients with COVID-19. The purpose of this study was to determine if lenzilumab correlated with better patient outcomes when compared to symptomatic care, corticosteroids, and remdesivir. A total of 520 patients were selected for this study. Patients with an oxygen saturation of less than 94% on room air, or those requiring supplemental oxygen were selected. Patients requiring invasive mechanical ventilation, such as endotracheal intubation, were excluded. Patients were randomly selected to receive lenzilumab, a monoclonal antibody that acts as an antagonist to granulocyte-macrophage colony-stimulating factor (GM-CSF), or a placebo. COVID-19 severity is strongly associated with GM-CSF and the C-reactive protein (CRP) inflammatory markers. GM-CSF is one of the mediators of the hyperinflammatory immune response and is associated with the progression and severity of COVID-19. By targeting GM-CSF, prevention of the hyperinflammatory immune response caused by the cytokine can decrease the possibility of tissue damage.

Patients were administered 1800 mg of lenzilumab, divided into three doses of 600 mg to be administered every eight hours. Patients in the control group received a placebo with corticosteroids and remdesivir over an intravenous infusion of one hour. The efficacy of lenzilumab was determined by the likelihood of survival without ventilation (SWOV). SWOV was determined if a patient had not required mechanical ventilation by day 28 of the study. (Temesgen et al., 2023). Patient comorbidities were included as variables identified as; diabetes, hypertension, coronary artery disease, congestive heart failure, asthma, COPD, interstitial lung disease, prior diagnoses of thrombosis or embolism, prior diagnosis of cancers, and chronic kidney disease. These comorbidities were identified as risk factors and incorporated into an

iterative multivariate logistic regression analysis, which showed a positive outcome in SWOV for patients receiving treatment with lenzilumab ($p< 0.001$). Secondary outcomes were identified as time of recovery, invasive mechanical ventilation (IMV), extracorporeal membrane oxygenation (ECMO), admission to the Intensive Care Unit (ICU), or death. Incidence of ECMO, IMV, or death was not statistically improved by lenzilumab in the overall patient population but was less likely when patients had a baseline CRP <150 mg/L.

For the patients receiving infusions of lenzilumab, a significant difference was seen in SWOV. One hundred fifty-two patients achieved SWOV, as opposed to 144 placebo-treated patients ($p< 0.001$) with baseline CRP levels of less than 150 mg/L. Patients with a baseline CRP level above 150mg/L experiencing hyperinflammation associated with COVID-19 are at increased risk of escalation in respiratory support or death. When compared to the placebo, lenzilumab decreased the possibility of invasive mechanical ventilation and increased the likelihood of patient survival ($p= 0.0403$).

During the hyperinflammatory response of COVID-19, elevation in interleukin-6 drives an increase in CRP. “Baseline CRP levels predict subsequent oxygen supplementation requirements in hospitalized patients with COVID-19 from 85 mg/L for those on low-flow O2 to 110 mg/L for those on high-flow O2; and 205 mg/L for those on invasive mechanical ventilation (IMV).” (Temesgen et al.) Significantly higher baseline CRP levels are noted in patients with worsening end-organ failure compared to patients without end-organ failure. Increased CRP levels are also linked to an increased risk of 30-day mortality. Patients with a CRP baseline level of 99 mg/L or less have a 21.5% 30-day mortality compared to a 39.2% 30-day mortality rate in patients with baseline CRP levels ranging from 100-400 mg/L ($p< 0.001$).

One of this study's greatest strengths was the evaluation of each candidate broken down by the patient's comorbidities, regardless of whether the patient received the lenzilumab or the placebo treatment. One weakness of this study was that Temesgen et al. did not evaluate lenzilumab's impact on mortality and focused on the association between IMV and mortality.

Safety and efficacy of Tocilizumab in the management of COVID-19

Sarhan et al. (2022) conducted a randomized cohort study consisting of 108 adult patients admitted to an intensive care unit with severe COVID-19 virus confirmed by PCR. The purpose of this study was to determine if tocilizumab is a safe and effective treatment option for patients infected with the COVID-19 virus. The patients who were suffering from a known cytokine storm were considered severe. Patient demographics such as age and gender were gathered. Clinical data such as exposure history, symptoms, and comorbidities such as coronary artery disease, arterial hypertension, chronic obstructive pulmonary disease, and congestive heart failure were also included. This information was then entered into a database which divided the groups randomly. Each group was administered a combination of medications that were then used in the patient's treatment regimen. The first group of 56 patients received treatment with 800mg intravenous Tocilizumab (TCZ) daily, as well as two 400mg doses of hydroxychloroquine (HCQ) for the first day of treatment. After day one, patients were given 200mg HCQ intravenously twice a day, for the remaining five days of the trial. Tocilizumab is commonly used in the treatment of systemic juvenile idiopathic arthritis as well as rheumatoid arthritis. The second group of 52 patients received a combination of TCZ and Remdesivir (RMV). These patients were given the same regimen of TCZ as group one. An initial dose of 200mg RMV was

administered intravenously on the first day of treatment. For the five remaining days of the trial, the dose of RMV was decreased to 100mg, infused over one hour.

Laboratory results were reviewed at the time of hospital admission. Baseline oxygen saturation, respiratory rate, and body temperature were some of the parameters measured between group one (TCZ-HCQ) and group two (TCZ-RMV) and showed no statistical significance. The TCZ-HCQ group had an average baseline oxygen saturation of 85%, whereas the TCZ-RMV group had an average of 82%. Average baseline respiratory rates were similar between the TCZ-HCQ group and the TCZ-RMV group averaging 29 breaths per minute (bpm) and 30 bpm, respectively. Similar body temperatures were also noted with the TCZ-HCQ group averaging 39 degrees Celsius and the TCZ-RMV group averaging 38 degrees Celsius.

C-reactive protein (CRP), Lactate Dehydrogenase (LDH), ferritin, and D-dimer are the inflammatory markers linked to the COVID-19 infection and were measured to gauge the efficacy of the medication combinations. The TCZ-HCQ group had a baseline average CRP of 97 mg/dL with an endpoint average of 26 mg/dL ($p< 0.001$). The TCZ-RMV group also showed a significant decrease in CRP with a baseline average of 125 mg/dL and an endpoint average of 20.1 mg/dL ($p< 0.001$). A significant difference was seen in the average LDH between the two groups with baseline averages for LDH in both the TCZ-HCQ group and TCZ-RMV group were 516 IU/L and 397 IU/L, with average endpoints reading 312 IU/L and 370 IU/L, respectively ($p< 0.049$). The TMZ-HCQ group showed a significant difference in serum ferritin with a baseline average of 540.5 ng/mL and an endpoint average of 337 ng/mL ($p< 0.001$). The TMZ-RMV group showed an increase in serum levels of serum ferritin with a baseline average of 673 ng/mL with an endpoint average of 1,044 ng/mL. D-dimer levels showed a baseline average of 0.48μg/dL in the TMZ-HCQ group, with an average endpoint of 0.23 μg/dL ($p< 0.001$). In the

TMZ-RMV group, a baseline average D-dimer showed 0.58 μg/dL. The average endpoint showed no statistically significant difference of 0.52 μg/dL ($p = 0.41$).

One of the strengths of this article was that the authors took advantage of the parameters they had access to. However, there were no endpoint numbers for oxygen saturation, respiratory rate, or body temperature. The authors seemed to rely more on the lab values than the vital signs of the patient. One of the weaknesses this article had was that they did not differentiate between patients who only had hypertension, coronary artery disease, diabetes, or chronic obstructive pulmonary disease. It is unclear to the reader what other comorbidities these patients had besides all the comorbidities listed across both groups of patients.

RECOVERY Collaborate Group (RCG, 2021) conducted a randomized, controlled, open-label platform trial from April 23, 2020, to January 24, 2021. The purpose of this study was to determine if tocilizumab is a safe and effective treatment for patients infected with the COVID-19 virus. Twenty-one thousand five-hundred fifty total patients initially enrolled in the RECOVERY trial consisting of three phases of treatment at one of the 131 trial sites in the United Kingdom. Phase one had 542 patients treated with dexamethasone, 557 patients treated with lopinavir-ritonavir, 383 patients treated with hydroxychloroquine, 2041 patients treated with azithromycin, 3,083 patients treated with colchicine, and 8,107 receiving the usual care protocol of the facility the patient was admitted to. Phase two had 5,285 patients receiving convalescent plasma, 2,416 patients receiving REGN-COV2, and 6,301 receiving usual care. In phase three of the trial, 4,450 patients were administered aspirin and 4,594 patients received usual care. Seventeen thousand four-hundred thirty-four of the original 21,550 patients did not proceed to the second randomization trial. Four thousand one-hundred sixteen patients would be randomly assigned to the RCG's upcoming trial.

The RCG evaluated the effects of tocilizumab in patients hospitalized with COVID-19 suffering from both hypoxia and systemic inflammation. If the attending physician believed treatment with tocilizumab would put the patient at substantial risk, they were excluded from the trial. Four thousand sixteen hospitalized patients were eligible for this study if they had laboratory-confirmed SARS-CoV-2 infection, or if COVID-19 was clinically suspected by the the attending physician. Eligible patients were divided in a 1:1 ratio using a web-based randomization tool. One group received the usual standard of care protocol the patient's hospital had set in place, and the second group received the usual standard of care plus tocilizumab.

Patients in the tocilizumab group were to receive an intravenous infusion of tocilizumab over one hour. Patients received their dose of tocilizumab based on their weight. Patients weighing over 90 kilograms would receive 800mg. Patients weighing less than 90kg, but more than 65kg received 600mg. Patients weighing from 40-65kg received 400mg, and patients weighing less than 40kg received a weight-based dose of 8mg/kg of tocilizumab. Patients were administered a second dose of tocilizumab 12-24 hours later if the attending physician did not believe the patient's condition had improved. Patient outcomes were assessed at 28 days, and again at 6 months after receiving treatment, with the primary outcome being all-cause mortality. Secondary outcomes included: time admitted to the hospital, receipt of invasive mechanical ventilation, or death.

At the time of randomization, 562 of the 4,116 patients selected were on invasive mechanical ventilation. One thousand six-hundred eighty-six of the 4,116 patients were on non-invasive ventilation such as high-flow oxygen via nasal cannula or non-rebreather or continuous positive airway pressure. One thousand eight-hundred sixty-eight patients were not receiving simple oxygen therapy and nine patients were not receiving oxygen. The 28-day follow-up form

was completed by 1,964 (97%) of the 2,022 patients in the tocilizumab group and 2049 (98%) of the 2094 patients who received usual care. "Among the patients with a completed follow-up form, 1,647 (84%) of 1964 allocated to the tocilizumab group and 77 (4%) of 2,049 allocated to usual care received at least one dose of tocilizumab (or sarilumab, another IL-6 antagonist). Five-hundred sixty-five (29%) of 1,964 patients in the tocilizumab group and 17 (1%) of 2,049 in the usual care group received more than one dose of tocilizumab (or sarilumab)." (RCG, 2021).

Tocilizumab administration showed a significant reduction in 28-day mortality when compared to the usual care group (621 of 2,022 in the tocilizumab group vs. 729 of 2,094 in the usual care group) ($p=0.0028$). Tocilizumab administration also showed a greater probability of patient discharge within 28 days of admission (1,119 patients in the tocilizumab group vs. 1,024 patients in the usual care group) ($p<0.0001$). Among the patients not on invasive mechanical ventilation, tocilizumab reduced the risk of patient progression to requiring invasive mechanical ventilation or death when compared to usual care (687 patients in the tocilizumab group vs. 861 patients in the usual care group eventually needing invasive mechanical ventilation) ($p<0.0001$).

One strength of this article was the large sample size the RCG was able to use for this study. One weakness was, that while they were able to have this large sample size, there is no data as to which patient received what treatment in the first three phases of the trial. Another weakness was having a physician determine if the patient had improved. It is difficult to objectively evaluate the subjective opinions of one individual.

Safety and efficacy of Garadacimab in the management of COVID-19

In 2020, Papi et al. (2023) conducted a randomized, double-blind, placebo-controlled, parallel-group study from July 1st, 2020, to January 12th, 2021. The purpose of this study was to

determine if garadacimab could be used as an effective treatment for patients infected with COVID-19. The study was conducted across 14 sites in the United States of America. Patients were at least 18 years of age, with a positive SARS-CoV-2 infection within 14 days prior to patient screening confirmed by polymerase chain reaction, interstitial pneumonia confirmed by a chest X-ray of CT, and the presence of COVID-19 that is considered severe 24 hours before screening. Patients were excluded from the study if they required endotracheal intubation and mechanical ventilation at the time of patient randomization. Patients who were actively bleeding, or at significant risk for bleeding, as well as a history of deep vein thrombosis were also excluded from this study. Baseline demographics and clinical characteristics such as age, height, weight, BMI, and COVID-19 characteristics were balanced between the two groups at the time of randomization.

One-hundred twenty-four patients were randomized in a 1:1 ratio with 63 of the patients receiving a 700mg intravenous dose of garadacimab and 61 patients receiving a placebo. Garadacimab is an IgG4 monoclonal antibody. This monoclonal antibody is an antagonist of the kallikrein-kinin pathway and specifically inhibits the coagulation factor XII. All patients were to receive the standard-of-care (SOC) treatment. Standard of care treatment consisted of both inhaled and intravenous corticosteroids, as well as heparin. The primary efficacy endpoint for this study was the incidence of patient progression to endotracheal intubation or death before endotracheal intubation by day 28 after randomization when compared to the placebo. Secondary efficacy endpoints included the use of continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP), the use of a high-flow nasal cannula, the median length of hospital admission, the incidence of endotracheal intubation from randomization to day 28, and all-cause mortality.

By day 28, the study population consisted of 117 patients, 58 of whom received at least one dose of garadacimab, and 59 patients who received a placebo. There was no statistical difference in the proportion of patients who progressed to endotracheal intubation or death before endotracheal intubation from randomization to day 28 between the patients who received garadacimab or placebo (22.2% vs 26.2% respectively) (p=0.274). The incidence of all-cause mortality was seen in 17.5% of patients who received garadacimab versus 18.0% of patients receiving placebo (p=0.382). Of the patients who received garadacimab, 19.0% were placed on CPAP/BiPAP versus 16.4% of patients receiving placebo (p=0.626). High-flow nasal cannula oxygenation was deemed necessary for 14.3% of patients receiving garadacimab and 18.0% of patients receiving placebo (p=0.382). There was no statistically significant difference in the length of hospital admission between the two groups (p=0.767).

Sixty-four point one percent of patients in this study experienced treatment-emergent adverse events (TEAE). Overall, patients receiving garadacimab experienced fewer TEAEs than the group receiving the placebo (60.3% vs. 67.8%). While most TEAEs were considered mild to moderate between both groups, 30 patients receiving garadacimab experienced a serious TEAE, whereas 45 patients receiving a placebo experienced a serious TEAE. The most frequently reported TEAEs that were deemed serious included: respiratory complications, vascular and cardiac complications, and infections.

One of the main strengths of this study was that Papi et al. were able to gather data from multiple facilities throughout the United States. One weakness of this study is that it is not established what standard of care treatment was used across all facilities and it is not defined what patients received.

Safety and efficacy of Adalimumab in the management of COVID-19

Fakharian et al. (2021) conducted a randomized control trial consisting of 68 patients at the Dr. Masih Daneshvari Hospital. The purpose of this study was to determine if adalimumab is a safe and effective treatment option for patients infected with the COVID-19 virus. Patients aged 18-70 with severe SARS-CoV-2 confirmed by Reverse-Transcription-Polymerase Chain Reaction (RT-PCR) and CT scans confirming bilateral pulmonary infiltration were eligible for this study. Severe cases of COVID-19 were determined based on a heart rate greater than 125 beats/min, SpO_2 less than 93% on room air, respiratory rate greater than 30 breaths/min, the need for invasive mechanical ventilation or vasopressors, and acute hepatic, renal, or neurological deterioration due to COVID-19. Patients were excluded from this study if they had a rise in serum creatinine greater than 0.3mg/dL in a 48-hour period, a glomerular filtration rate less than 30mL/min, a history of liver failure, heart failure, peptic ulcer disease, latent or active tuberculosis, a known allergic reaction to adalimumab, or any active infection.

Thirty-four patients were designated to receive adalimumab, and the remaining 34 were assigned to a control group. All patients in this trial received dexamethasone, remdesivir, and supportive care. Adalimumab is a monoclonal antibody that is a TNF-a antagonist and inhibits the interaction of TNF receptors on the p55 and p75 cell surfaces. The primary outcomes of this study were the requirement of invasive mechanical ventilation, admission to the Intensive Care Unit (ICU), and mortality rate. All of these outcomes were assessed until patient death or discharge from the hospital. Secondary outcomes were the length of the patient's stay in the ICU and improvement observed in the chest CT scan.

Data and symptoms were evaluated at baseline, day three, and day seven after adalimumab treatment. Overall, adalimumab did not prove beneficial in the treatment of patients

with COVID-19 infection when compared to standard-of-care treatment and showed no statistically significant difference between the groups evaluated. Four patients in the adalimumab group and three patients in the control group required invasive mechanical ventilation. Five patients in the adalimumab group and five patients in the control group required admission to the ICU. The mortality rate showed four patients in the control group and four patients in the adalimumab group. Patients in the adalimumab group had an average ICU stay of 13 days whereas patients in the control group had an average ICU stay of nine days ($p=0.53$). Eight patients in the adalimumab group and five patients in the control group showed greater than 50% improvement in their chest CT scans ($p=0.74$).

It is difficult to truly determine if adalimumab would be beneficial had more patients been involved in this study. It was hypothesized that adalimumab's TNF-a antagonistic properties would decrease the severity of COVID-19 and show better overall outcomes for patients. One strength of this study was how Fakharian et al. chose feasible, quantifiable evidence to base the effectiveness of adalimumab.

Safety and efficacy of Tixagevimab-Cilgavimab in the management of COVID-19

In February 2020, the ACTIV-3-Therapeutics for Inpatients with COVID-19 (TICO, 2022) Study Group conducted a randomized, double-blind, phase 3, placebo-controlled trial across 81 sites in the United States, Uganda, Europe, and Singapore. The purpose of this study was to determine if tixagevimab-cilgavimab is a safe and effective treatment option for patients infected with the COVID-19 virus. Patients over the age of 18, hospitalized with confirmed SARS-CoV-2 infection, whose symptoms were present for up to 12 days were chosen for this study. Patients were excluded from this trial if they required IMV, ECMO, had acute organ

failure, required vasopressor therapy, renal replacement therapy, or mechanical circulatory support.

One thousand four-hundred fifty-five patients were randomly divided into two groups in a 1:1 ratio. Patients were to receive either a single dose of 300mg tixagevimab-300mg cilgavimab combination administered over a 30-minute infusion, or a placebo. “Tixagevimab-cilgavimab is a combination of two Fc-modified human monoclonal antibodies derived from B cells from two individuals who had recovered from SARV-CoV-2 infection. These antibodies recognize non-overlapping sites on the receptor binding domain of the SARS-CoV-2 spike glycoprotein” (ACTIV-3 TICO Study Group 2022). Remdesivir was administered to all patients unless contraindicated. Corticosteroid use was encouraged for patients with hypoxemia, and all other medications were administered in accordance with the facility's standard of care protocols.

The primary efficacy outcome of this study was focused on the time from patient randomization to sustained recovery up to day 90. Secondary efficacy outcomes included a seven-category pulmonary ordinal outcome scale, length of hospital admission, a composite, sustained recovery up to day 90, and all-cause mortality up to day 90. The final population analyzed included 1,417 patients, 710 of whom were to receive a complete or partial infusion of tixagevimab-cilgavimab and 707 who received a placebo.

At day 90, no significant difference was seen when comparing sustained recover. Eighty-nine percent of patients in the tixagevimab-cilgavimab and 86% of patients in the placebo group achieved sustained recovery (p=0.21). At day 90 a significant difference was seen when comparing death between the two groups. Death occurred in 61 (9%) patients who received tixagevimab-cilgavimab versus 86 (12%) patients in the placebo group (p=0.032). There was no statistical difference in the proportion of participants across the pulmonary ordinal scale

categories on day five (p=0.52) or day 14 (p=0.15). However, tixagevimab-cilgavimab was favored on day 28 (p=0.0024). Serious adverse events, incident organ failure, serious co-infection, and death were identified as the main safety outcomes in this study. At least one safety outcome occurred in 178 (25%) patients in the tixagevimab-cilgavimab group and 212 (30%) patients in the placebo group (p=0.059). Overall, tixagevimab-cilgavimab was better tolerated among patients with lower rates of treatment-emergent adverse events (TEAE) and showed a 30% reduction in mortality risk up to day 90.

One strength of this study was the large sample size of patients as well as a much longer primary efficacy outcome of 90 days after medication administration when compared to many other trials. Since this was phase three in a much larger trial, it is not stated what medications patients received prior to starting this phase of the study.

Discussion

Based on the above research, it can be determined that there is a benefit to using certain monoclonal antibodies in the treatment of COVID-19 when compared to SOC. There are three common goals throughout most of the studies regarding the use of monoclonal antibodies in patients with COVID-19. The first goal is to decrease the length of hospital admission, the second is to decrease the severity of symptoms that may be lethal to more fragile patients, and the third is to reduce the overall mortality of COVID-19. The true efficacy of monoclonal antibodies is difficult to determine due to SOC treatments differing across facilities. It is also difficult to determine if patients who were part of much larger and longer trials benefitted from the treatments from previous trials vs. the trials where monoclonal antibodies were used alone.

Of the analyzed studies conducted by Avdeev et al. (2021), Temesgen et al. (2023), and Sarhan et al. (2022) in the literature review, inflammatory markers showed significant decreases in patients who received netakimab, lenzilumab, and tocilizumab. Tocilizumab and netakimab were associated with a lower mortality rate when compared to all other monoclonal antibodies in the literature review (Temesgen et al., 2023). Netakimab, tocilizumab, lenzilumab, and tixagevimab-cilgavimab showed greater efficacy in decreasing the length of hospital stay and a decrease in overall mortality (TICO). Garadacimab and adalimumab appeared to be the least effective monoclonal antibodies regarding infection with COVID-19 (Papi et al., 2023). Garadacimab was shown to be ineffective in decreasing mortality rate, length of hospital admission, and decreasing the incidence of patients requiring either CPAP or BiPAP (Papi et al., 2023). Adalimumab did not show a decrease in the length of hospital admission or a decrease in the likelihood of ICU admission (Fakharian et al., 2021).

The number and severity of adverse events recorded were shown to be similar across all trials of monoclonal antibodies when compared to standard-of-care treatment. However, it is difficult to determine how truly severe these adverse events were since the severity of the symptoms was subjective. There were no incidences of anaphylaxis in any of the studies analyzed in the literature review.

Applicability to Clinical Practice

While this project focuses on the use of monoclonal antibodies on patients admitted to the hospital, there could be a potential for these infusions to be performed as an outpatient procedure in the clinic. These monoclonal antibody infusions could be administered to patients who do not meet the criteria for hospitalization but are still considered at high risk of severe disease

progression. Outpatient monoclonal antibody infusions would use fewer resources than hospital admission and could lower the cost to the patient significantly. The studies have shown the risk of severe adverse reactions is low and the severity of the disease has also become reduced with certain monoclonal antibodies. If resources allow, patients could also potentially receive monoclonal antibody infusions in their own homes. Community Paramedics and Home Health Nurses can administer these infusions and monitor patients for adverse reactions. Having these infusions as outpatient procedures could reduce the rate of hospital admissions as well as lower the risk of spreading the infection to other patients and providers. Medical providers should continue to encourage high-risk patients to receive the COVID-19 vaccine as well as practicing proper handwashing and disease prevention.

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