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Mini Review

COVID Monoclonal Antibodies and Current Research: Are We There Yet?

Enrique Arredondo[1], George Udeani[2] and Salim Surani[3]*

[1]*Second-Year Professional Student, Irma Lerma Rangel College of Pharmacy, Texas A&M University, Texas, USA*

[2]*Head and Clinical Professor, Department of Pharmacy Practice, Irma Lerma Rangel College of Pharmacy, Texas A&M University, Texas, USA*

[3]*Adjunct Clinical Professor, Texas A&M University, Texas, USA*

***Corresponding Author:** Salim Surani, Adjunct Clinical Professor, Texas A&M University, Texas, USA.

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Abstract

With the coronavirus disease 19 (COVID-19) causing a health crisis worldwide, researchers and clinicians are exploring different pharmacological treatments to fight against this pandemic. A leading class of drugs currently being experimented with to treat, prevent, or decrease the severity of COVID symptoms are monoclonal antibodies. Many pharmaceutical companies are constructing monoclonal antibodies by utilizing the antibodies produced by patients infected with COVID. By analyzing the antibodies' structure and using the mechanism of action of how COVID infects the host, specific and compelling monoclonal antibodies targeting the virus's pathway to infect the cells can be constructed. Regeneron and Eli Lilly and Company are two leading pharmaceutical companies currently working on monoclonal antibodies. Regeneron is currently working on a combination monoclonal antibody known as REGN-COV2. The combination therapy has shown to reduce both viral levels and improve symptoms in non-hospitalized patients. In contrast, Eli Lilly and Company's combination of bamlanivimab and etesevimab has shown to reduce viral load, symptoms, COVID-related hospitalization, and emergency room hospitalizations. This minireview aims to bring awareness of the different clinical trials involving monoclonal antibodies and their current status.

Keywords: Monoclonal Antibody; Neutralizing Antibodies; COVID-19; SARS-CoV-2; Regeneron; Bamlanivimab; Etesevimab; REGN-COV2

Abbreviations

COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; SARS-HCoV: Severe Acute Respiratory Syndrome Human Coronavirus; MERS-CoV: Middle Eastern Respiratory Syndrome Coronavirus; ACE2: Angiotensin-Converting Enzyme 2; CCR5: C-C Chemokine Receptor Type 5; mAB: Monoclonal Antibody

Introduction

The novel coronavirus disease 2019 (COVID-19) was first reported in Wuhan City, Hubei Province, China, when citizens were admitted to the hospital for pneumonia with unknown etiology. It was not until January 7th when COVID-19, also known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was identified by a group of Chinese scientists through genome sequencing [1]. Coronavirus is a large family of viruses that have been around for decades. COVID-19 is an enveloped virus that contains a single-stranded positive-sense RNA. It belongs to the Coronavirinae subfamily and the Betacoronavirus genera along with two highly pathogenic viruses; severe acute respiratory syndrome human coronavirus (SARS-HCoV) and Middle Eastern respiratory syndrome coronavirus (MERS-CoV) [2-5]. Clinical symptoms may manifest as fever, cough, shortness of breath, pneumonia, and may range from mild to severe.

The human body can gain immunity from infection of a pathogen through either passive or active immunity. Passive immunity is protection from infection through antibodies obtained either naturally or artificially. Examples of natural passive immunity is antibodies being passed through the placenta to the child while artificially is through vaccinations [6]. Active immunity is when the host produces the antibodies after being infected with the pathogen. When the body gets exposed to a pathogen, white blood cells known as B cells create antibodies and memory cells. When the body is then exposed to the pathogen the second time, the immune system can quickly fight off the infection [7].

How does coronavirus infect the host?

Using this same concept and applying it to the coronavirus, monoclonal antibodies can be a promising and effective treatment option. Monoclonal antibodies are laboratory-made versions of antibodies that respond to invading pathogens [8]. The use of monoclonal antibodies has been gaining traction in their use as they are an effective method for providing highly specific targeting therapy for particular diseases [9,10].

To construct effect monoclonal antibodies for COVID-19, the mechanism of action on how the virus infects the body must be understood first. A research team in China has been able to identify that COVID-19 has a similar envelope spike protein receptor-binding domain to that of SARS-CoV despite there being some variation in amino acid residues [11]. This similarity has led to the suggestion that COVID-19 has binding affinity for the host angiotensin-converting enzyme 2 (ACE2) to infect the cells, the same mechanism as SARS-CoV [12]. The glycoprotein spikes on the surface of COVID-19 utilize the membrane ACE2 receptors to enter the host cells acting as a target site [13-16].

Current research with monoclonal antibodies

To address the recent update on the monoclonal antibodies, lets' address some monoclonal antibodies to treat which is making the headlines in the media. Regeneron is a biotechnology company that is currently working on an anti-viral antibody cocktail, REGN-COV2, to treat and prevent SARS-CoV-2 infection. REGN-COV2 cocktail consists of monoclonal antibodies REGN 10933 + REGN 10987. The combination of the monoclonal antibodies has been shown to reduce viral levels and improve symptoms in non-hospitalized COVID-19 patients. The randomized, double-blinded trial measured the effect of adding REGN-COV2 to the usual standard of care compared to adding a placebo to the standard of care. The preliminary data released by Regeneron Pharmaceuticals consisted of 275 patients that were randomized in a 1:1:1 ratio. Group 1 received a one-time infusion of 8 grams of REGN-COV2 (high dose), group 2 received 2.4 grams of REGN-COV2 (low dose) and group 3 was assigned to the placebo. Table 1 breaks down the demographics and characteristics of the patient population involved. Some key findings identified in the study were: REGN-COV2 rapidly reduced viral load through day 7 in patients that tested negative with SARS-CoV-2 antibodies (seronegative), more significant reductions in viral load at day 7 in patients with higher baseline viral levels, and patients who had an absence of COVID antibodies and/or had higher baseline viral levels also had significant results in symptom alleviation [17-19]. With the promising results shown in the preliminary data analysis, led Regeneron to submit a request to the U.S. Food and Drug Administration for an emergency use authorization for REGN-COV2 an antibody combination therapy. In addition, safety, tolerability, pharmacokinetics, and immunogenicity are currently being investigated in a healthy volunteer study [20].

Regeneron patient demographics and characteristics	
Total Patients	275
Male	49%
Female	51%
Hispanic	56%
African American	13%
Have one or more underlying cause	64%
Average Age	44

Table 1: Demographics and characteristics of study population involving REGN-COV2.

Eli Lilly and Company (Co.) is another leading pharmaceutical company investigating their own monoclonal body drugs, bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016). Bamlanivimab is a neutralizing Immunoglobulin-G-1 monoclonal antibody directed against the spike protein of SARS-CoV-2, while etesevimab is a recombinant human monoclonal neutralizing antibody targeting the surface spike protein receptor-binding domain. On October 7th, 2020, the company provided a comprehensive review on their placebo-controlled, randomized, double-blind, Phase 2 clinical trial, also known as BLAZE-1. BLAZE-1 has demonstrated that the combination therapy reduced viral load, symptoms, COVID-related hospitalization and ER hospitalizations. Table 2 shows the clinical endpoints measured in the trial along with their respective p-values demonstrating statistically significant data [21,22]. This led to

Eli Lilly and Co. requesting U.S. authorization for emergency use but did not last long [22]. On October 13th, 2020, it was reported that Eli Lilly and Co. had halted their treatment due to an unknown potential safety concern [23]. This halt in the study shows the potential concerns involved when using monoclonal antibodies as a treatment option.

Table 3 below shows the different clinical trials that are utilizing monoclonal antibodies [24].

LY-CoV555 and LY-CoV016 Combination Therapy Data	
Reduced viral load at day 11	p = 0.011
The proportion of patients with persistent high viral load at day 7	Combination therapy: 3% Placebo: 20.8 percent P < 0.0001 without multiplicity adjustment
Time-weighted average change from baseline in total symptom score from day 1 to 11	Improvement of symptoms observed as early as 3 days after dosing it p = 0.009
Rate of COVID-related hospitalization and ER visits	Combination therapy: 0.9% Placebo: 5.8% Relative Risk Reduction: 84.5% (p = 0.049)

Table 2: Clinical endpoints and their respective p-values for combination therapy.

Clinical Trial	Study Design	Monoclonal Antibody	Mechanism of Action	Primary Outcome	Status	Current Phase
Crizanlizumab for Treating COVID-19 Vasculopathy (CRITICAL)	Placebo-controlled, double-blind randomized clinical trial	Crizanlizumab	Monoclonal antibody that targets P-selectin. Crizanlizumab can decrease inflammation by binding to P-selectin, blocking leucocyte, and platelet adherence to the vessel wall.	Soluble P-selectin level	Recruiting as of October 16, 2020	Phase 2
Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients - Sarilumab Trial - CORIMUNO-19 - SARI (CORIMUNO-SARI)	Cohort multiple Randomized Controlled Trials (cmRCT) design	Sarilumab	Human IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6Rs (sIL-6Rα and mIL-6Rα) and has been shown to inhibit IL-6-mediated signaling	Survival without needs of ventilator utilization on day 14. Group 1 WHO progression scale Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14	Active, not recruiting as of October 16, 2020	Phase 2 and 3

CORIMUNO-19 - Tocilizumab Trial - TOCI (CORIMUNO-TOCI) (CORIMUNO-TOC)	Cohort multiple Randomized Controlled Trials (cmRCT) design	Tocilizumab	Anti-human IL-6 receptor monoclonal antibody that inhibits signal transduction by binding sIL-6R and mIL-6R	Survival without needs of ventilator utilization on day 14. Group 1 WHO progression scale Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14	Active, not recruiting as of October 16, 2020	Phase 2
Study to Evaluate the Efficacy and Safety of Leronlimab for Mild to Moderate COVID-19	Two-arm, randomized, double-blind, placebo-controlled multicenter study	Leronlimab	Humanized IgG4, a monoclonal antibody to the C-C chemokine receptor type 5 (CCR5)	Clinical Improvement as assessed by change in total symptom score (for fever, myalgia, dyspnea, and cough)	Active, not recruiting as of October 16, 2020	Phase 2
Safety of TY027, a Treatment for COVID-19, in Humans	First-in-Human, Time Lagged, Randomized, Placebo-Controlled, Double-Blind	TY027	SARS-CoV-2 Monoclonal Antibody	Number of participants with treatment-related adverse events as assessed by CTCAE v4.0	Active, not recruiting as of October 16, 2020	Phase 1
Treatment with CSL312 in Adults with Coronavirus Disease 2019	Prospective, multicenter, randomized, double blind, placebo-controlled, parallel-group study to assess the safety and efficacy	Garadacimab	Factor XIIa Antagonist	The incidence of tracheal intubation or death prior to tracheal intubation	Recruiting as of October 16, 2020	Phase 2
Safety, Tolerability, and Pharmacokinetics of SCTA01, an Anti-SARS-CoV-2 Monoclonal Antibody, in Healthy Chinese Subjects	First-in-Human, Randomized, Double-blinded, Placebo-Controlled	SCTA01	Recombinant humanized anti-SARS-CoV-2 monoclonal antibody	Dose-limiting toxicity (DLT) Maximal Tolerable Dose (MTD)	Recruiting as of October 16, 2020	Phase 1
Study of TJ003234 (Anti- GM-CSF Monoclonal Antibody) in Subjects with Severe Coronavirus Disease 2019 (COVID-19)	Randomized, double-blind, placebo-controlled, multi-center trial to evaluate the safety and efficacy	TJ003234	Anti- GM-CSF Monoclonal Antibody	Proportion (%) of subjects experiencing deterioration in clinical status Treatment Emergent Adverse Events	Recruiting as of October 16, 2020	Phase 1 and 2
Phase 3 Study to Evaluate Efficacy and Safety of Lenzilumab in Patients With COVID-19	Randomized, double-blind, multicenter, placebo-controlled clinical trial	Lenzilumab	Anti-human GM-CSF monoclonal antibody	Time to Recovery	Recruiting as of October 16, 2020	Phase 3

A Study of AK119 (Anti-CD73 Antibody), a Treatment for COVID-19, in Healthy Subjects	First-in-human (FIH), single-center, randomized, double-blind, placebo-controlled	AK119	Humanized monoclonal antibody targeting the CD73	Incidence of treatment-emergent AEs [Time Frame: From signing of informed consent till end of study (approximately 64 days post dose)]	Recruiting as of October 16, 2020	Phase 1
VIR-7831 for the Early Treatment of COVID-19 in Outpatients (COMET-ICE)	Randomized, Multicenter, Double-blind, Placebo-controlled Study	VIR-7831	Anti-SARS-CoV-2 monoclonal antibody	Proportion of participants who have progression of COVID-19 through Day 29 [Time Frame: Up to Day 29]	Recruiting as of October 16, 2020	Phase 2 and 3
Compassionate Use Open-Label Anti-CD14 Treatment in Patients With SARS-CoV-2 (COVID-19)	Expanded Access	IC14	Recombinant chimeric monoclonal antibody (mAb) recognizing human CD14, to block CD14-mediated cellular activation in patients early in the development of ARDS	Test the safety and potential efficacy of IC14 treatment in preventing the progression of severe respiratory disease in patients hospitalized with COVID-19	Expanded Access Status: Available	Expanded Access
Study of CPI-006 as Immunotherapy for Hospitalized COVID-19 Patients	Single-dose, dose-escalation study is an open label trial evaluating the safety	CPI-006	Humanized monoclonal antibody targeting the CD73 cell-surface ectonucleotidase	Incidence of Treatment-Emergent Adverse Events to Determine Single Dose of CPI-006 That is Safe in Patients with COVID-19 Immunoglobulin Anti-SARS CoV-2 Levels	Recruiting as of October 16, 2020	Phase 1
Study of Mavrilimumab (KPL-301) in Participants Hospitalized With Severe Corona Virus Disease 2019 (COVID-19) Pneumonia and Hyper-inflammation	Interventional, randomized, double-blind, placebo-controlled study encompassing 2 development phases (Phase 2 and Phase 3).	mavrilimumab	Anti-granulocyte-macrophage colony-stimulating factor receptor alpha (GM-CSF-Rα) monoclonal antibody (human isoform immunoglobulin G [IgG4])	Cohort 1: Proportion of Participants Alive and Without Respiratory Failure at Day 15 Cohort 2: Mortality Rate at Day 15	Recruiting as of October 16, 2020	Phase 2 and Phase 3
A Study to Assess the Efficacy and Safety of Gimsilumab in Subjects with Lung Injury or Acute Respiratory Distress Syndrome Secondary to COVID-19 (BREATHE)	Multi-center, adaptive, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of gimsilumab	Gimsilumab	monoclonal antibody against granulocyte macrophage-colony stimulating factor (GM-CSF), which is a myeloid cell growth factor and pro- inflammatory cytokine	Incidence of mortality	Recruiting as of October 16, 2020	Phase 2

Table 3: Current clinical trials reported in ClinicalTrails.gov involving monoclonal antibodies targeting SARS-CoV-2.

Conclusion

Since the start of the coronavirus pandemic, many researchers and clinicians have been resorting to testing different drugs that may benefit the patients. Monoclonal antibodies are a promising biological drug class that can potentially make a breakthrough in treating the current coronavirus disease-2019. However, historically the way scientific research has been presented to the public and other clinicians is by going the peer review, publish the findings, then present the information to the media and public. Now the information reaches the media and public before it even goes through the peer review and publication process. To maintain the integrity of science and provide accurate information to the public, it is imperative to maintain the process of getting all current clinical research peer-reviewed before publication. By skipping this process, the media can influence how the information is presented, leading to unproven claims about specific COVID-19 treatments that can mislead the public.

Conflict of Interest

The authors whose names are listed, certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this review manuscript.

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