Transcript Details

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Fight COVID-19 with Neutralizing mAbs

As of February 2022, information originally presented in the original broadcast has been updated. Due to the rise of the omicron variant, two combination therapies no longer carry EUA: bamlanivimab+eteseviman and casirivimab+imdevimab.

Announcer:
Welcome to CME on ReachMD. This activity, titled “Fight COVID-19 With Neutralizing mAbs” is provided in collaboration with Forefront Collaborative and AKH and supported by an educational grant from Lilly.

This replay of a live broadcast discusses how clinicians can overcome challenges in the treatment of COVID-19.

Since the presentation-recording, the Assistant Secretary for Preparedness and Response (ASPR) paused all distribution of bamlanivimab+etesevimab and etesevimab alone (to pair with existing bamlanivimab supply). Two additional changes of note: dosing of casirivimab+imdevimab decreased to 600 mg of each compound; EUA criterion pertaining to BMI was reduced to 25.

Here’s your moderator, Dr. Mimi Secor.

Dr. Secor:
Hi. I’m Dr. Mimi Secor and I’d like to welcome to the program Dr. Marilyn Bulloch, Associated Clinical Professor of Pharmacy Practice at Auburn University, Harrison School of Pharmacy and the University of Alabama at Birmingham School of Medicine in Tuscaloosa, Alabama, Dr. Robert Gottlieb from the Center for Advance- Advanced Heart and Lung Disease at Baylor University Medical Center, Baylor Scott and White Research Institute in Dallas, Texas, and Ms. Tesha Seabra, Associate Director in the Department of Medicine at the Cedars-Sinai Medical Center in Los Angeles, California, they’re going to join me in discussing the use of mono- neutralizing monoclonal antibody therapy in the outpatient treatment of patients with COVID-19. Welcome, everyone.

Dr. Bulloch:
Thank you for having us.

Ms. Seabra:
Thank you.

Dr. Gottlieb:
Thank you.

Dr. Secor:
Please note, faculty disclosures are available on the event page and are listed on this slide. During this activity you will hear from our multidisciplinary faculty as they share clinical trial information, best practices and real experiences from their own institutions. You’ll have a chance to claim credit by completing an evaluation after participating in the course and have your questions answered live during a question and answer session.

Dr. Gottlieb, infection rates have been going down in the United States, but are now starting to tick up in some states, what are, what have we learned in the past year that can inform our approach to COVID-19, now?

Dr. Gottlieb:
Thank you, Dr. Secor for that question. If we could bring up the first slide, please. And if you'll skip to the next, thank you.

So, this is a different era from where we were at just one year ago. One year ago, when COVID-19 was starting to progress across the country, the guidance that we gave our country per- people was, "Stay at home unless you need hospitalization", that we didn't have anything for them, we were just starting to get testing and we didn't know what was going to happen. Now, we are informed by a year of progressive accumulation of data and expertise and how best to manage this, how the virus behaves, what to expect and we are now in a new era where we have outpatient effective, safe therapies for COVID-19. COVID-19 is a deceiving name, first of all, I'm fortunate that this is COVID-19 rather than say, COVID-2021, it's not supposed to be here, this year, but we'll move on past that. But different people have a different constellation of symptoms, especially early on. And that mix and match of symptoms may deceive somebody. A lot of patients say, "Gosh you know, my family member but they also had pneumonia", well, COVID pneumonia is the hospital disease that we're trying to prevent. Patients often have a window where they're either early in the disease process, perhaps mildly symptomatic that might be an opportunity to intervene on changing the o- the course of their illness. They may think themselves too well, but we really, we need that extra time to know what's coming down the pike and unfortunately, we don't' have that personalized nature of medicine, yet, we don't know what the future holds, we just have statistics, and we can predict with certain risk factors, who's at greater risk. But if something happens to one individual the opportunity to have intervened was always earlier. So, it's all about the virus and the host and we don't' know exactly how that interplay occurs until after the fact.

Next slide.

During the course of last fall, when and winter, we were fortunate to have a total of 3 emergency use authorization neutralizing monoclonals informed by phase 2 randomized placebo-controlled trials. Since that time, we now have phase 3 data, as well, and I'm gonna reference later on in the talk. And Dr. Bulloch is gonna go over the criteria for the emergency use authorization. And Ms. Seabra is gonna share best practices of how to administer these.

The first therapy that was authorized is bamlanivimab, and that was on November 9th, followed in close succession by the combination therapy of casirivimab and imdevimab, together, and then most recently in early February, we've seen the combination of bamlanivimab and etesevimab together authorized and in fact, in the last week the FDA has started encouraging us to use the bamlanivimab and etesevimab combination together, in lieu of monotherapy bamlanivimab and is now issuing etesevimab vials to match and complete the set for bamlanivimab to make that combination, together.

We're gonna go through the data that has led to the emergency use authorizations and further data that actually supports the efficacy and clinical use of why you should be advising patients earlier in their disease process to consider these therapies. Because ultimately, the decrease hospitalization and risk of death and we now have that data emerging from phase 3 clinical trials for the combination therapies.

Next slide.

The purpose of a combination is to target the virus in more than one spot and give it more than one therapy that it has to try to escape from to make the therapy itself more enduring. On the left here, we have bamlanivimab alone where mutations of specific point mutations, for example glutamine 44, lysine E44K and the others listed here can decrease the inhibitory concentration 50 and titer the avidity of the neutralizing monoclonal antibody for the virus, allowing the virus to have the potential to start escaping. Now, if you add a second antibody together, it makes it more challenging to escape from both antibodies at the same time and indeed, instead of being two orders of magnitude down, it's less than 1 order of magnitude down with these mutations for etesevimab and that gives us the hypothesis that combination therapy will be more enduring as well as limit the escape and help address variance.

Next slide.

Dr. Secor:
Well, Dr. Gottlieb, how do these data, how do those data translate to the therapy that is appropriate to give to patients?

Dr. Gottlieb:
Well, the most important thing to know about this is the opportunity as we'll go and explain and share it is most evident early in the disease process. The analogy I would draw is if you're house is burglarized, the opportunity to capture that burglar is when the burglar is just entering or is in your house and you hopefully noticed on a security camera. If you're out of town on vacation and you come back and you see that your house has been burglarized, there's very little chance of capturing that burglar after they've already had a week to intervene. That's really what we're talking about here, the opportunity to intervene and prevent progression to COVID-19 pneumonia requiring hospitalization as early on in the disease course and I recommend my patients capture that opportunity if they're eligible for a

therapy.

Dr. Bulloch, what are your thoughts?

Dr. Bulloch:
I agree. I think the earlier that you start these drugs, the better off these patients do. We know that that's true with all anti-infectives. We have that data from really most infectious disease processes up to this point and it stands to reason that it would continue with COVID-19. Ms. Seabra?

Ms. Seabra:
Yes, I agree. You know, in our institution, it's really like a therapy that we give to our patients. It has to do a lot with the inventory that we have currently that is coming to our hospital. So, it varies, and it changes but if you have, you know, primarily it will help if we give the most appropriate therapy to the patient. Back to you, Dr. Gottlieb.

Dr. Gottlieb:
Thanks. So, let's bring up the next slide.

So, the purpose of the next few slides is to share the phase 2 data that informs the basis for the subsequent phase 3 data the phase 2 data is really going to discuss virologic activity, but ultimately what all of us wanna know, as clinicians, is what is the clinical efficacy? So, let's build that story one-by-one. Let's start with the phase 2 data.

The, this is the story of casirivimab and imdevimab together from Regeneron and the purpose of this graph here is to show that patients early on in the disease that haven't had time to generate their own antibodies will actually have a virologic benefit from the combination infusion. And so, these are antibody negative patients on the left early on in the disease and you have a significant additional benefit of virologic clearance on top of the natural history of virologic clearance and really what you notice also is the highest titers are early on in the disease, either in that pre-symptomatic or early symptomatic phase. Now, on the right, these are patients that we thought were within seven days of symptoms but in the end, they probably had it longer because they were already serum positivize on enrollment; they didn't recognize that they had actually had the infection for longer and when you add antibodies to endogenous antibodies, you no longer have the additive effect, because the disease is already progressing to that next stage. You're either destined to worsen or destined to recover on your own.

Next slide.

This is another way of looking at that, another surrogate for early disease is the viral titer. When you have the highest viral titer on the far right, you have the most pronounced virologic effect and this was studied at two dosing levels of the casirivimab/imdevimab combination. You see, just to the left of that at 10 to the 6 copies, you still have that pronounce virologic effect for both dosing levels whereas as you come down on copy number and your further on your disease, likely the virologic effect is attenuated, such that on the far left, you actually don't see a virologic effect when a patient enters the trial having a lower viral load and that suggests that they've actually had the disease longer. So, the opportunity to have the virologic effect is early on in the disease.

Next slide.

What we also saw was from bamlanivimab and etesevimab together, this is the Eli Lilly combination neutralizing monoclonal and we saw a natural trend towards clearance of the virus in most patients between day 3, 7 and 11, in fact, that may inform some of our quarantine recommendations. But what you see on the far right is the of each panel is the gray bars of the placebo and next to that in mustard yellow, you see the combination. The combination of bamlanivimab and etesevimab together has virologic activity detectable as early as day 3, persisting to day 7 and that the primary endpoint at day 11 is statistically significant for a virologic effect and that was thus the dose that was chosen for an additional phase 3 data that I'll go on to show you.

Next slide.

Dr. Secor:
So, Dr. Gottlieb, we're gonna hear soon about this specific EUA criteria that would make a patient appropriate for neutralizing monoclonal antibodies based on the presence of certain risk factors. How do you approach patients, especially now, as, as people are feeling optimistic about the vaccines becoming increasingly available will their symptoms, when their symptoms do not qualify them for a hospitalization that they should go and get infusion therapy?

Dr. Gottlieb:
Well, I think it's important to educate patients and their healthcare providers that we now have the evidence-base and that's what I am gonna walk you through the following slides because a lot of people say, "OK, great, you have virologic effect, what I really care about

is, is it gonna help my patient decrease their risk? Is it gonna help my patient recover? Is it gonna help prevent death of my patient? And is it gonna help them avoid hospitalization?". So, let's walk through that.

Next slide.

Here's the hypothesis that early on in the disease when you have outpatient early mild-to-moderate COVID-19, the disease is a virally driven disease that is susceptible to antiviral to actually alter the future course, whereas late in the disease, using the analogy to the burglar where the burglar is already out of the home, the damage is already done, and the cascade is already set in motion and the opportunity is already closed on antivirals working. So, we've actually studied clinical trials through clinical trials as both in inpatient and outpatient settings so I'm gonna walk you through the outpatient trials of BLAZE-1, as well as that was from Eli Lilly as well as the Regeneron version for their combination.

The criteria are slightly different, slightly different, but overall similar and the phase 3 clinical trials use the original emergency use authorization criteria that have been slightly modified in the interval. In BLAZE-1, the criteria was to enroll within 3 days of the first positive test and in fact, typically, patients were about 4 days from symptoms and Regeneron patients had to be within 7 days of the first symptoms. The hypothesis here is late in the disease, that the COVID-19 is actually potentially virally uncoupled, and you've lost that window. If someone is sitting at home with influenza, we ask them to try to get an antiviral early in their disease course, within the first 48 hours. The analogy is here, although testing takes some time, we would recommend a patient that meets the criteria for the EUA consider the emergency use authorization, neutralizing monoclonal antibodies early in the disease process when they don't require hospitalization with an intent to decrease their risk to need hospitalization.

Next slide.

So, let's talk about the phase 3 data. So, BLAZE-1 is the multi-part trial that now has phase 3 data available. Regeneron has now also released their data in the past week or so, but the data is very complimentary. BLAZE-1 was the Eli Lilly bamlanivimab and etesevimab combination. This is real, large, clinical trial, randomized data where you have bamlanivimab plus etesevimab together in a combination of 2,800 mg of each versus placebo, 1,035 patients.

Dr. Secor:
Mmm.

Dr. Gottlieb:
The primary endpoint is, could we decrease the risk of progression to hospitalization for CO- COVID-19 or all cause death. And here what you see in gray, you actually have the natural history, where about 7% of the patients that had high risk factors, meeting and EUA criteria, progressed to hospitalization or death whereas only 2.1% of patients that were treated with the active bamlanivimab and etesevimab combination together progressed. That was a 70% risk reduction and in fact, there were about 12 deaths in the trial, they were all in the placebo arm and none in the active arm, so we can say that this actually does seen to prevent death, as well.

On the right, we ask the question, could we use a lower dose because we thought we were already at saturating doses, could we use lower dose preserve the antiviral efficacy and clinical efficacy and potentially reach more patients with a limited supply and the answer is yes, this is the first half of that data and about midway through this, we were detecting about an 87% risk reduction in 29 day hospitalization and all cause death in this trial. These are two, sequential phase 3 portions of a trial and then coupled together with the Regeneron data from casirivimab and imdevimab together this week, also showing a 70% risk reduction in a comparable comparatively designed trial, we now have three different data points that all say, "Yes we actually don't have just virologic activity, but we can actually clinically help the patients".

Next slide.

However, if a patient waits too long and they're hospitalized, this is the data from the first arm of the active three NIH clinical trial asking will neutralizing monoclonal antibodies have efficacy in the inpatient setting? And just as we referenced before, once you're hospitalized, the disease seems to be virally uncoupled or at least, that's what I believe, and in this case, the neutralizing monoclonal antibodies did not change the time to sustain recovery or chance of hospital discharge in patients hospitalized with severe COVID-19. So, this frames the a- the discussion, informs us on the disease, that a patient sitting at home saying, "Am I sick enough?", the answer is you actually have symptoms, you're in the window where we an intervene, if you wait too long, we may not have that window.

Next slide.

So, in summary, we now have, not only phase 2 clinical trial data, but we have phase 3 clinical trial data that really forms the basis of current and future emergency use authorizations that the neutralizing monoclonal antibodies indeed can decrease the risk of hospitalization, ER visits or death when given within 72 hours of the diagnosis. The EUA criteria that Dr. Bulloch is gonna reference are

a little broader to allow practicality in administration. These have not been demonstrated to have efficacy once a patient requires hospitalization for COVID-19, so the window is early. And then the effect seems to be more dramatic in higher risk patients and in those that have not had the chance to generate their own antibody response suggesting once again, the early window is the best. They appear to be safe and well-tolerated, and Dr. Bulloch is gonna discuss in her portion how to safely administer them the, and then Ms. Seabra is also gonna share her practical experience in a large, urban center.

Back to you. So, let's actually move on to the polling question. So I'll read this off. A 57-year-old perimenopausal female with a body mass index of 34.9 calls your office to report 5 days with chills without fever and associated myalgias but absent cough. She followed your advice and bought a pulse-oximeter last year, just in case. Her pulse oximetry is 95% on room air. She had a positive rapid SARS-CoV-2 direct antigen test just today at a drive-through test center. She asked you, as her healthcare provider to call in a prescription for ivermectin. I will say, before you move on to answer this question, I want to inform you that in our clinical trials, we actually specified that a body mass index of 34.5 specifically rounded up to 35.

Dr. Secor:
Alright, polling question number 1. What do you recommend? A) Ivermectin and strict quarantine, B), social isolation and keep checking her pulse ox, hospitalization if the PS02 is 90 or less, C) neutralizing monoclonal antibody therapy if she develops a fever or cough, counsel her if she is not sick enough to qualify, D) it is too late for neutralizing antibody monoclonal antibody therapy as it has been over 48 hours since her symptoms began, E) arrange neutralizing monoclonal antibody therapy with bamlanivimab together with etesevimab the following day, F) repeat the test, as COVID-19 diagnosis requires PCR rather than direct antigen test?

Dr. Gottlieb:
Dr. Secor, I think our audience has nailed it. So this is great. No one fell for any of those foils. So, the manufacturer acknowledges that ivermectin does not work. A year ago, we had a temptation to use therapies just because we didn't have any. Now we have therapies we can use evidence-based therapies. The manufacturer of ivermectin does not recommend its use and it us made public comments along those lines.

In terms of the social isolation, sit at home and wait for your pulse ox to drop, not only is that not the right choice because she does qualify for neutralizing monoclonal antibodies, but the second portion, here, I want to emphasize is that this is a SARS virus. unlike other viruses where you can wait 'til someone has an oxygen level of 90%, the definition for many trials of severe COVID-19 usually has a cut point of 93 to 94% and that's the time that I actually recommend a patient consider hospitalization, particularly if they're not usually requiring oxygen and sitting at 93%. She does qualify and it is early, so I do recommend going ahead and considering the neutralizing monoclonal antibodies at the earliest opportunity, in this case, a wait of under a day is certainly reasonable, if you can get it the same day, great. Back to you, Dr. Secor.

Dr. Secor:
Thank you, Dr. Gottlieb. I'd now like to introduce Dr. Bulloch.

Dr. Bulloch:
Hi.

Dr. Secor:
How are you doing?

Dr. Bulloch:
Good, how are you?

Dr. Secor:
Good. So, speaking of identifying appropriate patients for neutralizing monoclonal antibody therapy, can you review the EUA criteria for use?

Dr. Bulloch:
I'd be happy to. Can we go to our next slide? And then the one after that, there, there we go.

So, I think what's important to understand, as Dr. Gottlieb, kind of, iterated several times is these drugs are meant for outpatients with mild disease whose oxygen saturation is still good; they're not requiring oxygen, or if they're on baseline oxygen like some of our COPD patients have, it has, their demand hasn't gone up. And what we're really trying to do is to keep them from progressing to severe COVID-19 and requiring hospitalization, having, sort of, the downward spiral we know can occur. And so, when the FDA put together the EUA, they really looked at who was high risk for that progression. Now, the group of patients that I tend to see the most in my practice fall in this left-hand category over here. they're, they're geriatric, or maybe they're obese with a BMI over 35, they have CKD or diabetes, or

they're immunosuppressed, so either physiologically or we did it to them with some, sort of, medicine. I also see a fair share of people who qualify 'cause they're a little bit younger, they're over the age of 55 but they have some, sort of, chronic pulmonary or cardiovascular disease. There is an allowance for use in adolescence, those between 12 and 17, as long as they're at least 40 kg and that 40 kg is really important because we know that adolescents have different pharmacokinetics and pharmacodynamic parameters which can affect the way their bodies process and respond to a drug, and so, that's an important thing to remember. But beyond that, the FDA looked at things that they thought qualified and adolescent for progressing to severe COVID-19. The one I think most people are gonna see most frequently is gonna be children or adolescents who have some, sort of, chronic pulmonary disease that are on chronic medications. I know in my area of the country, I'll tend to see a lot of sickle-cell disease, but they really did, sort of, look to see who, who was at high risk for progression.

You also want to take into consideration, these are not FDA-approved regimens. They're still experimental and in order to use them, you have to explain their risk versus benefits to patients and get consent from either the patient or their designee.

Next slide, please.

Also, I want to go through some just some considerations for treatment administration. These all target the receptor binding domain of the spike protein on the virus, but they target different areas. And as Dr. Gottlieb mentioned previously, this can be very helpful in terms of making sure that we're able to cover several of the variants that we know have emerged. But another concept behind this combination therapy is not only are we hoping to make sure that we can cover the variants that are already out there but maybe even prevent future treatment-emergent variances from developing. The doses that are, exist right now may change we're seeing more data, they're looking at different combinations and as, what we're using now when the dose, if these drugs do get FDA approved, they may or may not be dosed the same way we're using now.

Pregnancy is a consideration that I think is worth mentioning because many people who work outside of OB have a tendency to want to avoid medication used during pregnancy, we're not very comfortable with it. But remember that these are fully-human IG antibodies, and so unlike monoclonal antibodies that may be created to using mice, these are more natural, and people are less likely to have reactions to them. And while there's no data in pregnancy with either one of these regimens, yet, in general IGG products are not withheld in pregnancy. So, if you have a woman who's pregnant who otherwise would qualify, she certainly should be considered for one of these regimens.

On the other hand, pediatrics is a little bit more debatable. The American Academy of Pediatrics takes a difference stance than the FDA. They just put out a paper that specifically recommends against the routine use of these drugs in children, primarily because we don't have a lot of data on how they work and how, what their safety is in adolescents and we do have to remember that they have different pharmacokinetics and pharmacodynamic parameters. And until that information is available, they just don't feel comfortable recommending them, routinely. There's also the consideration that there's conflicting data about exactly what does put an adolescent at high risk for progressing to severe COVID-19. The one guideline for COVID-19 that has been consistently a living document is the NIH guidelines and they've made a couple of different points regarding both regimens. For casirivimab/imdevimab, they say at this point, they don't feel that there's enough published data and data points to make a stance one way or the other. They can't say that is works, but they can't say that it doesn't. There has just recently been some more data provided, they may update their recommendations from that, but we'll have to wait and see.

On the other hand, with bamlanivimab and etesevimab, they do feel that it has been studied in enough patients and with enough clinical data points that they felt comfortable making an evidence-based recommendation to use these in people who qualify.

Dr. Secor:
Dr. Bulloch, how do you connect patients with a provider who administers neutralizing antibodies?

Dr. Bulloch:
That's such a great question and one that I think is emerged a lot over the last few months. Can we do to my next slide and we'll look at ways we can do this.

When they first came out, I feel like they were probably isolated to specific centers and with big health systems but they, it has expanded quite a bit and now infusions are authorized in a, a wide variety of settings, everything from clinics to the emergency room, even you can take them to nursing homes, I've heard of places, even going right into the patient's home and infusing them. A lot of big health systems do have integrated clinics and their own infusion centers, and this is wonderful, especially if you live in a big metro area or somewhere near a large academic medical center or health system. But it can still be difficult for those clinicians who work in small towns or rural areas that aren't integrated into these health systems. So, health and human services created a website that is very easy to use. You just log in, you put in your zip code and what driving range you're willing to go to, and it will show you everywhere within that

range that has received a shipment of one of these regimens. Now, it's just shipment data, there's no guarantee that they're actually infusing at the certain times that you want, but it's a great starting point.

And National Infusion Center Association also provides a list of infusion centers that are providing monoclonal antibody therapy, but it's not based on shipment data, so there's no guarantee that they received an allocation that week or they're gonna have any supply. But also, a great starting point when you don't' have a point of reference.

If you happen to be in a place where you feel like, I have enough patients that I, I would be able to administer this, you can do that, the government is providing the medication and it's using a single wholesaler, an AmerisourceBergen, so you can go onto their specific website, put in your information, they'll contact you in order to make that happen.

Dr. Secor:
Alright. Dr. Bulloch, what other requirements or barriers to administering an antibody therapies outside of an infusion center, such as a long-term care center or a residential facility?

Dr. Bulloch:
Yeah, it's such a great thing to talk about because we have expanded where we have gone with these infusions and how we're able to administer them outside of just your traditional infusion clinic. Can we go to the next slide and we'll walk through this process.

So, these drugs all have to be refrigerated until they're prepared and even once they're made up, they really need to be refrigerated until it's time to use. And so, if you happen to be at a clinic or somewhere that's gonna administer them onsite, it's best just to wait to prepare the infusion until the patient gets there and has IV access. Once they arrive, you want to go ahead and escort them to their room make sure that you're, kind of, isolating them from everybody else and everyone's wearing their appropriate PPE. But you can make them up ahead of time. It's just when you make them, you just want to give them a chance to get to room temperature so when they infuse into the patient, they're comfortable. They're all gonna go in normal saline, it just depends on which drug and which volume. Now, consistently you can put them in 250 mL of normal saline, though that can differ according to what regimen you're using.

With casirivimab/imdevimab, each drug comes in its own 11.1 mL vial. But you're only gonna take 10 mL from each vial. But, in order to get the right concentration, you need to take 20 mL out from your infusion bag, so that you're not having you know, more fluid than you need to and get the right concentration. With bamlanivimab and etesevimab, it's a little bit different. Here, you can use lower volumes of fluid as low as 50 mL bags, i- but you're gonna be adding 60 mL, 20 mL from three different vials, and you don't have to take any out from the infusion in order to get the right concentration. What's nice is that you can administer these drugs either by pump or by gravity, as long as you have the right filter with casirivimab/imdevimab, you're gonna give it over 60 minutes. with bamlanivimab and etesevimab it really depends on the final concentration if the smaller volume that you're using, the faster you can give it. So, if you're using that 50 mL bag, you can give it as quickly as, you know, 21 minutes. You can consider longer infusions, particularly in delicate heart failure or CKD patients as well as those who might've had really mild infusion-related reactions, there's no guidance, exactly on what longer means. There is some guidance in lower weight patients, those who weigh between 40 and 50 kg with bamlanivimab and etesevimab they can give that over 70 minutes, instead of 60. But the thing, the really important thing to remember is the stability. These drugs do need to be refrigerated once they're prepared with bamlanivimab and etesevimab, you can put them in the refrigerator for 24 hours and then they're stable at room temperature for up to 7 hours. With the Regeneron product, you can refrigerate them for up to 36 hours but they're only stable at room temperature for ar- 5 hours. And that time does have to include the infusion period, as well.

Now, while you're infusing them, just for safety, you have to make sur that you get vital signs at baseline and every 15 minutes throughout both the infusion and through the 1 hour monitoring period.

Dr. Secor:
For those of you just joining us, this is ReachMD. I'm Dr. Mimi Secor and joining me to talk about neutralizing monoclonal antibody therapies for outpatient COVID-19 treatment are Dr. Bulloch, Dr. Gottlieb, and Ms. Seabra. I want to encourage our viewers to submit questions for them. You don't' have to wait until the end of the presentation. Also, there will be four more questions polling questions and the next one is coming right up.

Dr. Bulloch, what do we need to watch for in monitoring patients after having received an infusion?

Dr. Bulloch:
Well, luckily these drugs seem to be well-tolerated, as you can see on my next slide. Most people do really well at them, they don't even notice that anything is happening during the infusion. There have been some cases of nausea or bleeding or bruising, soreness around the injection site, with bamlanivimab and etesevimab, they've had some dizziness, itching or rash. With the Regeneron product, they have seen some vomiting, but one, I just want to point out is hyperglycemia. So, if you have a patient who's a sensitive diabetic, you may wanna monitor glucose a little bit closer.

Thankfully, the risk of severe adverse effects is rare, but it's still there, so while they're giving the infusion and for the hour afterwards, you need to watch for anaphylaxis and infusion-related reactions. They have been associated with clinical worsening after drug in-administration, but to be fair, the symptoms that patients experience also seem to correlate with progression of COVID-19. So, we haven't really been able to definitively say was this the drug or was this the disease? But certainly, as we use these drugs more, we'll get a clearer picture on that. But should you have a patient who does have a severe reaction, or there's a medication error that occurs, you must notify both the FDA and the manufacturer within 7 calendar days.

Next slide.

Dr. Secor:
So, here's the polling question I was just talking about. To date, what has been your biggest challenge in using or recommending the neutralizing monoclonal antibody therapy? A) understanding what patients would qualify for treatment, B) locating where patients could receive therapy, C) trying to find the balance between the goal of preventing COVID-19 disease progression with vaccination efforts.

I'm giving you a couple more seconds to answer and then Dr. Bulloch will review the possible answers.

Dr. Bulloch:
Well, I certainly hope we've been able to help people locate them. Let's talk about the balance between vaccination and antibody therapy with my next slide.

Now, this is something that hasn't necessarily been studied, but in theory, the monoclonal antibodies could reduce our body's immune response to the vaccine and that's not what we want. We want to be able to build that immunity. If you have somebody who's been full or partially vaccinated, who unfortunately does develop COVID-19 and they qualify, go ahead and give them the antibody. The vaccine doesn't seem to have any impact on the antibody's mechanism of action. It's just the reverse. For those patients who are using the two-dose vaccine series, you do have to wait three months after the monoclonal antibody administration to get your second dose, because remember, we want to give that vaccine a fighting chance to build full immunity. But once you do, you don't have to restart the vaccine series. You can just get your second dose, and those who haven't been vaccinated yet, at all, will just wait that full 90 day window after antibody infusion before they get vaccinated.

Next slide.

There may also be cases of patients who might need these drugs more than once. Particularly because we think that use of antibody therapy may technically attenuate the body's endogenous immune response, meaning that while we may prevent them from progressing to severe COVID-19, they may not develop that natural immunity to the virus and could get reinfected. Now, there's no data or case reports on recurrent use of these antibodies, it's just a, a theoretical at this point. We do know that the drug's half-life is about 3 to 4 weeks, so you're probably OK between that. There's also the consideration about variants, as Dr. Gottlieb went over, different drugs may cover different variants, and so if you have a patient who does seem to be reinfected, that would be something you would wanna think about. But in general, you wanna take each case on a case-by-case basis.

Dr. Secor:
Dr. Bulloch, thank you for the thorough overview.

As we move into our last section of the presentation, Ms. Seabra will go into more detail about her institution's program and walk us through a case. As a reminder, we have three more polling questions coming up as part of this case.

Ms. Seabra, your practice is at a large medical center that sees a diverse population of patients. What are your institutional goals in implementing a neutralizing monoclonal antibody infusion program?

Ms. Seabra:
Hi, good evening, Dr. Secor. So, yes so we did open our unit mid-November and really the institutional goals was to decompress the ED to reduce the number of hospitalizations and to increase the rate of survival, since our hospital was at the time at full capacity.

Next slide, please.

So, on this slide, we just shows our volume from mid-November 'til now. We're doing an average of 10 to 15 cases a day, which doesn't seem a lot, but because of the turnaround time of the rooms needing about 3 hours, it did require that length of time for the patient to be in the room. So, with a total volume, we considered a total volume that was 783 and still counting because we still doing infusions today. We did completed a total of 414 infusions. 369 were not infused because 315 did not meet criteria and primarily because patients tested more than 10 days ago or did not meet criteria as previously discussed by Dr. Bulloch. 23 of these case patients did cancel their infusion and a lot had to do with the lack of knowledge, the patients were scared, they had a lot of questions, and they preferred to manage their

symptoms by going to self-quarantine. 12 were referred to other agencies like home health because they were unable to come to the unit due to their mobility, 11 were referred to other med therapy facilities because of distance or because we're closed on the weekends and only operating Monday to Friday, only. 7 patients were hospitalized because of symptoms progression and 1 patient actually ended up expiring and that made us look into our workflow and actually start opening on the weekends, as well. And just having that Monday through Sunday operation.

Next slide.

Dr. Secor:
Ms. Seabra, how has your institution worked with long-term care facilities to expand access to neutralizing monoclonal antibody therapies?

Ms. Seabra:
So, actually on the next slide, we'll be able to look into that. So, we started doing a lot of outside referrals. So, initially we're seeing a large percentage of patients that required patient transport or they're coming from nursing homes or rehab facilities. They did require a lot of coordination and a lot of man-power, as well, even though, initially, the rooms were single-occupancy only, eventually, we also allowed caregivers, family members to accompany the patient, to defer the risk of falls. So, as more facilities start infusing the med therapy here in California, we are also able to collaborate and coordinate he care of these patients.

So, as the initial order came into us, we'll triage the patients via phone we'll perform an independent living assessment and that will determine the need for our site, home infusion or long-term care facility infusion. We'll then refer the patient to the case management team, which will then connect the patient and the family with the best and safest option for the patient, as well.

Next slide, please.

So, now we gonna go over a case scenario and this is Rose, she's 88 years old, she has a history of coronary artery disease, diabetes, and hypertension. She tested positive for COVID-19 and her doctor entered an order for neutralizing MAB therapy. The scheduler called her for a same-day appointment. The patient is hard of hearing, seems slightly confused on the phone, she passed the phone to her daughter, who told the scheduler that both her parents have COVID-19 and that her dad, he's much sicker than her mom. However, since they do have COVID-19, the daughter acknowledges that her parents should quarantine for 10 to 14 days and then she'll call back and schedule for the infusion.

Dr. Secor:
So, polling question. The scheduler A) agrees with the daughter and tells her to call back in 10 to 14 days after quarantine, B) educate the daughter that the infusion has to occur within 10 days of symptom onset, C) or a positive test, D) tell the daughter that her parents do not meet criteria for neutralizing monoclonal antibody therapy, E) tell the daughter to call her mother's doctor and change the order to a later date after self-quarantine, F) tell the daughter that if patients, if patients have mild symptoms, they do not need neutralizing monoclonal antibody therapy.

Ms. Seabra:
Yeah, so-

Dr. Secor:
I think we have a consensus.

Ms. Seabra:
Yeah, the consensus. So, this is correct. We educated the daughter that the infusion has to occur within symptom onset. And this is because a lot of our patients, they still assume that, that the message it is to quarantine 10 to 14 days they think they should have the infusion only after those 10 to 14 days have passed.

Next slide.

So, now they daughter understands but now tells the scheduler that we should have received the order for both her parents. We tell her that at this time, we only have the order for the mom and that we have an opening for the afternoon. She asks if her dad can take the mother's spot, since he's sicker and not doing well. The dad, is 91 years old, history of hypertension, lung cancer in the past, he had photodynamic therapy two years ago and he's currently in remission. We call pharmacy and are informed that the order for the dad was just approved. The problem is that we only have one spot left.

Dr. Secor:
How do we proceed? A) schedule the mom because her order came in first, B) schedule the dad since he's sicker, C) schedule both at

the same time in the same room D) schedule dad for the following day, E) tell the daughter to take dad to urgent care or ED.

Ms. Seabra:
Yes, so, in this case, we did schedule both at the same time in the same room and again, this was one of the ways that we changed our workflows to accommodate as many patients as possible. So if they patients were from the same household, we started doing double-room occupancy, like husband and wife, or a parent and daughter or, or son.

So, next slide.

So, now, both husband and wife are placed in the same room and they're happy to be together. While starting the IV on the wife, the nurse notices that she's diaphoretic. She states that she feels lightheaded. When checking vital signs, the heart rate is in the 40s, systolic blood pressure in the 70s, the patient has a 10 second loss of consciousness. We recheck the vital sign and her heart rate and BP are back to baseline. She doesn't know what happened and she feels weak, but otherwise, OK.

Dr. Secor:
How should the nurse proceed? A) call the physician, get an order for blood sugar test, B) call the crisis team and send the patient to the ED, C) cancel the infusion, send the patient home, D) draw labs, check and EKG, E) do nothing and proceed with the infusion.

Ms. Seabra:
Wow, that's correct. We do call the MD and do a blood sugar check. A lot of our patients because of their comorbidities, they require medical management. So, we'll rely on our medical director and many times we have to call the primary MD for the patient if the condition was related to the patient's medical history.

Dr. Secor:
We have a smart group, here, tonight.

Ms. Seabra:
Yes, we do. (laughter)

Next slide.

So, in conclusion, we should immediately screen all COVID-19 positive patients for possible MABS infusion. The infusion is most beneficial early in the infection. Be familiar with the screening guidelines and educate your coworkers on the importance and the use of MABS. Be an advocate for your patients and be persistent and assess for the possibility of home infusions.

Thank you.

Dr. Secor:
Thank you, Ms. Seabra. This has been a great way to round out our discussion on neutralizing monoclonal antibody antibodies for the treatment of COVID-19. I want to thank my colleagues, Dr. Gottlieb, Dr. Bulloch, Ms. Seabra for helping us better understand the key role of physicians, PAs, pharmacists, nurse practitioners and nurses in this challenging topic. It was great speaking with you, today.

Dr. Bulloch:
Thanks for having us.

Ms. Seabra:
Thank you.

Dr. Gottleib:
Thank you for the opportunity.

Announcer:
You've been listening to a replay of a live broadcast about neutralizing mAb Treatment in COVID-19. This activity was provided in collaboration with Forefront Collaborative and AKH and supported by an educational grant from Lilly. To receive your free CME/CE credit or to download this activity, go to ReachMD.com/CME. This is CME on ReachMD. Be Part of the Knowledge.