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Treatments for Outpatients With Mild-to-Moderate COVID-19

Announcer:
Welcome to CME on ReachMD. This CME activity titled: Treatments for Outpatients with Mild to Moderate COVID-19 is brought to you by AKH, Incorporated, Advancing Knowledge in Healthcare, and the American Thoracic Society, and is supported by an educational grant from GlaxoSmithKline. Before starting this activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Albertson:
Hello, this is Tim Albertson, Distinguished Professor of Internal Medicine from the University of California Davis in Sacramento. Welcome to another episode of The Rapidly Changing COVID-19, The Role of Monoclonal Antibodies Talk Series. Today we're going to be talking about the treatment for outpatients with mild to moderate COVID-19.

The learning objectives are to state the role of monoclonal antibodies in the treatment of coronavirus disease 2019, COVID-19 for short, and compare and contrast current monoclonal antibody treatments available in the United States, the emergency use authorization EUA with regard to administration, adverse events and efficacy, select appropriate candidates for monoclonal antibody treatment from mild to moderate COVID, and talk about healthcare disparities and how they may affect the incidence and severity of disease for this particular disorder.

The agenda then sort of follows. We're going to talk about an overview of SARS-CoV-2, talk about monoclonal antibodies, mechanisms of actions, options, how they're administered, the adverse events associated with their use, the role of monoclonal antibodies in the treatment of mild to moderate COVID-19. We'll talk more about who are the candidates for these monoclonal antibodies, and what kind of factors we can use in selecting other - the various monoclonal antibodies and other treatments that may be available. And then we will continue this discussion about healthcare disparities and give a summary.

Treatment selection, treatment strategies differ for outpatients versus those with severe disease who require hospitalization. Really look at it as a continuum of two distinct stages. The early stage is mild to moderate stage, and this is an outpatient stage characterized by a profound viral replication of the SARS-CoV-2 virus requiring some sort of antiviral therapy or symptom control. Antibody-based treatments that focus on minimizing viral replication would be appropriate at this timeframe. But as we - that disease process moves on, later stages where the severe disease may manifest, often require hospitalization. At this point, really, we think we're into a hyperinflammatory state, with very small reproduction of viruses going on compared to the amount of amplification of inflammation. And this is more in range of immunomodulator therapy time and supportive care. So there's really there's two phases and that's why in general, monoclonal antibodies are probably the most successful in the early phases of therapy as they relate to specific monoclonal antibodies that address CoV-2.

Health disparities. We tackled this one early on, but this is not a small area, this is a huge area. When we look at this in terms of the risks of infection, hospitalization, death by race and ethnicity, you can see some profound changes here. These are all in comparison to white non-Hispanic persons with cases, hospitalizations all go up for First Nation, other people, Asians, black or African Americans and Hispanic. In all three categories, both cases, in hospitalizations and deaths.

A number of reasons for these disparities, no single races have been shown to be immune to COVID-19 and the pandemic. But a lot of the disparities are probably related to lower socioeconomic status, poor efforts in prevention, and poor opportunities for diagnosis, management, and treatment. Pandemic has disproportionately affected people of color, people living in poverty, people with lower socioeconomic status, and people with underlying comorbidities. The strategies - the prevention strategies often are not available to people who are living in high-concentration areas. And this also the failure to be able to get vaccinations into some of these communities is another reason why they probably are at increased risk.

So, minority groups are often employed in lower central workers with continued exposure, fewer of them can work from home and limit their exposures. There has been less social distancing. In our area, we have a number of Asian immigrant families who are first generation. There may be 10, 15 in a single apartment, family members. So the social distance distancing in that kind of density of living is impossible. They have less access to healthcare, and there's probably going to be more homeless components and people in prisons and overcrowding communities as a result. So a number of reasons are thought contribute to these disparities.

But I look at it age as another disparity group. This is the risk of death by age groups. And the relative risk of death is 10.6 times higher if you're 85 or older. And it certainly marches out with increasing age. So, age is clearly a risk factor, and the death rate is despair - shows disparities there.

Comorbidities, obesity, diabetes with complications, chronic kidney disease, COPD, bronchiectasis, neurocognitive, coronary artery disease, all singularly offer an increased relative risk to death from COVID and represent another group of disparities. When you start putting these together in multiples, you can see very high rates of mortality with comorbidities.

So racial disparities may reflect the underlying health conditions that predispose to infection such as obesity, diabetes, cardiovascular disease, hypertension, kidney disease. Some of these are found higher in specific ethnic and racial groups. Some populations have higher rates of medical comorbidity often.

In retrospective observational trial - studies have found that higher rates of obesity and diabetes and black patients resulted in higher rates of COVID hospitalization in these groups. Early evidence reported a lower percentage of African Americans being tested for COVID-19 in those higher rates, of much lower rates of appropriate treatment. And recent studies have found comparable mortality once blacks and whites are hospitalized. But some of these changes occurred pre-hospitalization in the rates of disparities. So lots going on in this area, and it continues to evolve.

Monoclonal antibodies for the treatment of COVID-19. Specifically, we're talking about monoclonal antibodies that are developed from a single B cell clone. And they are designed to recognize the unique epitope. And that epitope, as it relates to COVID-19, is on the spike protein in the receptor-binding domain here.

And you can see these are examples of some older monoclonal antibodies that are this cartoon binding to the spike protein. With that binding, they then prevent that spike protein from linking up with the angiotensin - converting angiotensin-I, converting enzyme-II, which is the critical entry point that starts the process of enveloping that virus inside the human soul to allow reproduction. So this is a critical component, and if it can be blocked, then we can mitigate the factors that will lead to the severity of disease.

So this is the rationale of using monoclonal antibodies. And clearly by this mechanism of action, you can see that the earlier interface with the antibodies, the better the likelihood they are to have an impact on the disease. So again, it's pretty much what I said, the early earlier the stage the mechanism of action supports their interaction with the virus at an early stage to prevent the reproduction and amplification of the viruses.

Once the virus has amplified already and turned on the hyperinflammatory component of this disease, then it obviously is going to have much less of an impact on the overall outcome of the patient to effect multiplication of the virus at that time.

And EUA, emergency use authorization, is something that we haven't seen before this pandemic being used so readily, but the two and a half years roughly of this pandemic, we have seen so many drugs come and go. So many approaches come and go. So many EUAs being issued and then revoked, that it really has changed dramatically. Secretary of Health for Human Services is responsible for ensuring that these EUAs are appropriate. And it is a way to bypass the formal FDA approval process that literally for a new drug can take years. And as we've seen here, in two and a half years, we've seen many, many drugs approved on the EUA and a few drugs get FDA approval.

FDA approval now has been seen for a number of the vaccines and a few of the drugs that have been approved, but most of them are on EUA status for use in this pandemic.

One of the meaning treatments that are that are available as a monoclonal antibody face of Omicron BA.2 and the various sub-lineages that have come off of that, is bebtelovimab. And this particular agent is still approved for use of adults and adolescents greater than 12 years of age with weights greater than 40 kilograms that needs to be administered with within the first 7 days of symptoms. The dose of 175 milligrams intravenously. So this would be an outpatient treatment for mild to moderate COVID in the outpatient setting.

There's at least eight different monoclonal antibodies that are specific to the virus that have been a given EUA in the past or currently, the COVID-19. A list of them is also there. All are admitted as injections or infusions, and really required specialty infusion centers for the most part. Casirivimab and imdevimab previously could also be given subcutaneously, and this was certainly an advantage for that drug when it was effective. EUAs can be revoked and then they can be reauthorized as needed. So if the virus mutates back to a point where some of these previous monoclonal antibodies are again effective, then that EUA could be recertified.

As of January 24, 2022, the FDA temporary withdrew the EUAs and stopped distribution of casirivimab and imdevimab, and bebtelovimab and ___ 13:51, only to observe ineffectiveness in the dominant Omicron variant at the time. May 7th, sotrovimab also had its EUA revoked, and because of its lack of efficacy, as seen in the variants available at that time.

So this is sort of a summary of when they were - these various drugs were released, and an EUA was granted. Most of them that have been withdrawn, were withdrawn within 12 months of their initial issuance. So dynamic rapidly changing is a key point in the treatment of COVID-19, particularly with the use of monoclonal antibodies. Of these various combinations and single agents, only two are still available. And we'll go through - we've already talked about one, we'll go through the other combination drug, and how it plays a role in just a second.

So when we look at bebtelovimab and its side effects, it's pretty benign. Infusion related or hypersensitive reactions and less than point 3%, nausea in 0.8%, vomiting 0.7%, pruritis 0.3%, rash in 0.8%. So again, extremely well tolerated. It's an IgG monoclonal antibody and can spike protein of SARS-CoV-2. Binds to the spike protein and blocks attachment, as I've mentioned before with the other antibodies. It has been effective against Omicron sub-lineages also.

This is a graph that's a little hard to understand, but it looks at a bunch of different antibodies, and bebtelovimab is listed here. The further - the more dots you have to the right, the more insensitive the monoclonal antibody are, these are all variants of COVID-19. And so if you look at this particular one here, you can see that there's really nothing far to the right. And that's why this agent is still approved for the outpatient treatment of mild to moderate COVID-19.

This combination drug tixagevimab and cilgavimab, if you have any dyslexia, monoclonal antibodies will amplify them. So, I apologize in advance for the mind. This is a vaccination really, it is prophylactic antibody in patients who otherwise are not able to accept vaccination. So these are preventive monoclonal antibodies that are given pre-exposure prophylaxis. So, in general population for certain individuals who are either immunocompromised and the vaccine may or may not be effective, and those who cannot take vaccinations. This is a very small niche, but an important niche for prevention or mitigation of severity of COVID in compromised patients. So this would be a group of people who I'd be looking at who have received maybe the rituximab for rheumatological issues, or they're on chemotherapy, or they've had an adverse response to a vaccine, and they're not able to take vaccines. I think this is where this particular combination of monoclonal antibodies is really very useful and very - been playing a very important role.

This combination is two IgG monoclonal antibodies that are put together in combination with non-overlapping epitopes, so that they can bind in the protein receptor binding domain of the spike protein. And they block then the attachment to the human ACE2 receptor. They have a amino acid substitution to extend their half-life. And this is a key component, because normally monoclonal antibodies have fairly short half-lives 20 to 30 days. So they have to be often re-dosed on a monthly basis. This can go as long as 6 months. The dosing administration is two separate intramuscular injections, 300 milligrams of each of these monoclonal antibodies. So two shots intramuscularly. And it can be repeated every 6 months, if there's still significant risk of transmission. And certainly in my area, certainly in my house right now, there's a significant risk of transmission.

The FDA increased the dose in February 2022 from 150 milligrams to 300 milligrams of each of these agents. This is an unsteady dose, but it was based on in vitro studies, looking at the Omicron, and I'll show you some data to suggest this why this was the case a slide or two from now. The original study looking at this combination of monoclonal antibodies within 5,197 patients, with roughly a 2-to-1 active to placebo. And there was a profound 77% reduction in the risk of developing COVID as a result. So this is pretty significant data and was very impressive to the FDA to get an EUA issued quickly.

Side effects, pretty nonspecific, headaches, fatigue, cough, nothing that was overwhelming. There is some issue with severe cardiac AEs, a slightly higher rate 0.6% versus 0.2%. And just to remind you that statistics are usually not done on AEs unless they were predefined in a predefined way to collect them. So a spontaneous collection doesn't allow statistical analysis, whereas, if you have, in your study plan, put in a very detailed approach to how you're going to collect AEs, let's say cardiac AEs, echocardiogram every month,

arrhythmia, or EKG every week, something like that statistical analysis. But, so, this is a warning that people should be aware of, though there may be a slight increase in risk of cardiac AEs with the use of this prophylactic combination of monoclonal antibodies to prevent COVID-19.

And this is that same kind of graph that we looked at before, looking at the variants of COVID-19. And Evusheld is the name of the combination project at the top, and then each of the two specific monoclonal antibodies are listed. And you can see there's still quite a lot of variants that are way to the right, suggesting not the greatest coverage. And that's one of the reasons why this combination therapy is not approved for acute treatment, but still is thought to provide significant protection on a prophylactic basis.

Let's switch gears and talk about the role of monoclonal antibody in mild to moderate COVID in more detail. And some of the manifestations, I think everybody's pretty comfortable with this, fever, chills, shortness of breath, cough, taste and smell alterations, GI, nausea, vomiting, diarrhea. These appear within 2 to 14 days after exposure. I think the evidence is for the Omicron variants is more towards the 2 days than the 14 days at this point. May only require symptomatic supportive care, very minimal coronavirus is worst summer colds in the past. And so, certainly a lot of people now are not having a full-blown symptomatology, particularly with the penetrance of vaccinations in many of our communities.

Mild to moderate COVID 19 If a patient is at risk for regression to severe disease, if they are manifesting mild to moderate, they may be eligible then for anti SARS-CoV-2 monoclonal antibody therapy or oral antiviral treatments, which we will talk about. They must receive these therapies within 7 days for the monoclonal antibodies and within 5 days for the oral agents.

Severe COVID-19 requiring oxygen, requiring admission to hospital, and you know all the way to the ICU and ECMO and the whole gamut of it, unfortunate gamut, they have not been shown to provide any benefit with the use of monoclonal antibodies. So we do think the Omicron variant shortens incubation period of 2 to 3 days after exposure is more prominent, and that's why I mentioned that earlier. Upper respiratory including nose, mouth, throat with perhaps an increase in severe sore throat, headaches, dry cough, fatigue all can be seen with the Omicron variant.

Risk factors, age over 65, maybe even 55. More than 81% of the deaths are in the age group of greater than 65. Increasing risk of death as I've mentioned with underlying medical conditions, increasing numbers of comorbidities. Lack of complete vaccination. There still are people who do have breakthrough despite full vaccination. But I'll tell you our own experience has been right now that most of our patients are coming in with COVID into the hospital for other reasons rather than the COVID. And those that are coming in who are particularly severe, are often immunocompromised or patients who have not been vaccinated or not got a full set of vaccinations. Children and adults, particularly those with medical complexity, genetic issues, neurologic issues, metabolic conditions, certainly are also at increased risk. The list here of comorbidities that sort of outline the internal medicine practice, but these are all things that would put you at increased risk for developing severe COVID 19. Increased risk for it.

Medical conditions or treatments that may result in moderate to severe immune compromised, as I've mentioned before, puts you at risk, whether that's rheumatologic diseases or hematologic, solid tumors, liquid tumors, it's generally anything that might be affecting the immune system in a way that would deplete a B cell reactivity and T cell response. So HIV patients would be another group that might be at increased risk.

Vaccines are effective, there's no question about that. But they are not foolproof. But not everybody is vaccinated. When we look at the United States, maybe 66% of the entire country is fully vaccinated. And, you know, as every day goes by, boosters aren't obtained, and people fall off that list. So 77.27% have received at least in one dose, and 30.4 have had boosters. So really, there's an opportunity for breakthrough all the time. And much of that breakthrough is mild to moderate disease.

Disease progression from mild to severe can be rapid. So your interval for preventing that or at least reducing the risk of it is relatively short, and that's why the interventions have such short timeframes for the use. Bebtelovimab trial randomized phase 2 clinical trial that to mostly evaluate and low-risk outpatients. And 96% of the subjects enrolled in treatment or did not meet criteria for high risk. They received the combination of monoclonal antibodies, bebtelovimab and 27:56 ___ plus bebtelovimab, versus the single agent alone versus placebo. And the primary endpoint was a proportion of subjects with persistently high viral loads by day 7. And the study was designed for safety. It showed that bebtelovimab reduced time to sustain symptom resolution to 6 days versus 8 days, and was associated with a reduction in – well, reduction in the time for resolution. But very low incidence of hospitalization and death made it very difficult to show a difference there with this monoclonal antibody.

It does have that EUA as we've mentioned, and patients who require increasing baseline O2 therapy due to COVID, and those who previously were on chronic oxygen would also be those who would qualify. It's not a drug that should be given to patients who have known hypersensitivities to any of the ingredients in the therapies. And the FDA cautions against its use in hospitalized patients because - or patients were requiring high-flow oxygen or mechanical ventilation, because it hasn't really been shown to have any

efficacy in that group. And as we talked earlier on the mechanism of action, probably suggest it would not be effective once the hyperinflammatory component has kicked in.

Consider an antiviral the benefit most likely when given early after onset. Any sort of delay in diagnostic testing will potentially blunt its effect. Remember, testing kits now are widely available and can be obtained from the federal government. So, kit testing should not be a limiting factor in any population but getting the word out, having the technology to apply online to get it sent to your house, having a house to have it sent to, these are all things that might limit it. Monoclonal antibodies and the oral agents are not approved for hospitalized patients at this point.

The post-exposure prophylaxis, separate from the pre-exposure prophylaxis, was an area in which the other two combination monoclonal antibody products were approved. And when their EUAs were removed, their EUAs for acute treatment and post-exposure were pulled at the same time. So currently, we do not have monoclonal antibodies that have EUAs for post-exposure use at this time.

Homecare is all about hydration, fever control, supportive care, reducing infection transmission within the household if possible. And there's clearly changing rules regarding isolation and quarantine on a almost daily basis it seems, not quite. But I mean, work, isolation, and quarantine has changed dramatically from early in the pandemic currently. Some hospitals have even reached down and said the nurses who have the active COVID but are on the mend can come in and wear N95 masks can still do some nursing care. These are changing rapidly. But anything that can be done within a family, within a household to reduce the transmission, clearly is to the advantage.

Let's talk a little bit about antiviral treatments. We sort of mentioned around the edges a little bit, but let's go to more in detail about this as it relates to COVID-19. One of the major ways in which we can affect this viral load early on is using a protease inhibitor. The cartoon here shows you how an RNA virus in the cell co-ops some of the mechanisms for reproduction of RNA, and then builds itself from some of the apparatuses of the intercell matrix and endoplasmic reticulum to form a new virus. One place in there, there's inhibitors that can prevent the main formation of the M-pro agent and that critical proteolytic cleavage that occurs.

And so those drugs have been discovered and have been made available. The one that currently is used - one of them that is currently used as nirmatrelvir, and it's packaged with ritonavir to slow down its metabolism. So the second agent really is an inhibitor of metabolism to prolong the half-life. This has been made available after a phase 2/3 trial showed a substantial absolute risk reduction of 6.32% with 95% confidence intervals listed there of 34:21___ 3.59. This was in 2,246 patients randomized, that received the agents versus placebo. They had at least one risk factor. And they showed that they were substantially better off with this agent than without it. The adverse events were fairly minimal at 6.6 with placebo and 1.6 with the active antiviral agent.

So the indications for this agent now are greater than 12 years of age, 40 kilograms, have one risk factor for progressive diseases, and less than 5 days, not on a pre-prophylactic monoclonal antibody, not hospitalized, and not less than 12. So what they're advising is the use of nirmatrelvir two tablets 300 milligrams, with

100 milligrams of ritonavir one tablet, and all three tablets taken together twice a day for 5 days.

And the mechanism is again thought to be through the protease inhibition that’s critical. But the ritonavir blocks the cytoplasm 3A4, CYP3A4, and allows the half-life to be prolonged.

So a number of drug interactions can occur as a result of having the ritonavir to block the metabolism. So this then makes the clinician have to look through and make sure that they're not on a number of these agents that might have a significant drug interaction listed on the left. And then it can also there can be an induction of metabolism from the combination of antivirals. And this can lead to reduced levels of certain drugs on the right here.

So these agents are not without some concern and complexity, and really need to be thought out before they're just given. This is not a Tamiflu, it needs to be really patient-specific evaluations done.

Patients who have had reduced GFRs 30 to 59 milliliters per minute, that dose goes down to 150 milligrams, one tablet, and then one tablet of the ritonavir twice a day. And then anything less than 30 milliliters per minute, dialysis patients, etc., should not be getting this drug.

Another one of the antiviral agents that has come out is a molnupiravir, and this introduces lethal mutagenesis into the RNA virus. It has a half-life of about 3.3 hours and minimal metabolism, and clearances through the urine. This was the MOVe-OUT trial that got this drug the EUA. They looked at 1,433 multinational patients who completed analysis. They received 800 milligrams by mouth twice a day versus placebo. They were vaccinated, had greater than one risk - greater than or equal to one risk factor. Median age is about 43. So they tended to be a little bit younger. Obesity 74%, relative risk reduction is about 30%. There were 9 deaths in the placebo group. So that's a pretty high number for 1,433 outpatients. And one in the molnupiravir group. The AEs that were seen with this drug were

diarrhea 2%, nausea 1%, and then dizziness 1%.

The FDA EUA is 200-milligram capsules dosed at 800 milligrams by mouth every 12 hours for 5 days. You have to have the risk factor for progressive disease. You have to be within less than or equal to 5 days of the onset of symptoms. And it has to be other appropriate treatments are not available. In our area, this drug is not receiving a lot of use. It's not for prophylaxis. It's not for post-exposure. It's not for hospitalized patients. It's not for the less than 18-year-olds. In sexually active males and females, it's concerning. And there is some concern for, you know, genetic effects, genetic toxicity as a result. So very limited use in our area of this drug, but certainly it's important to know it's out there and available.

The last antiviral I wanted to chat about for outpatient use in COVID-19 is remdesivir. And this is a drug that has been approved early on in the pandemic for use in the inpatient side in the United States. The World Health Organization study failed to show an efficacy, so we don't see a lot of use of it outside of the United States. A few countries have adopted it, but not many. But this is a use as a outpatient drug.

It was a study called PINETREE. Non-hospitalized within 7 days of symptoms, had to be over 12, had to have more than or equal to one risk factor, and unvaccinated. They were given three days of remdesivir at 200, the loading dose and then a 100 the second day and 100 the third day, all I.V. They had 552 patients. It was terminated early. The mean age was 50. The mean symptoms were 5 days, 41.8% Hispanic or Latinx. The adverse events appear very safe like remdesivir. The adverse events were about 42% for remdesivir and 46.3% for placebo. And no measurable virologic impact was seen. But 47 fewer hospitalizations per 1,000 patients treated. And there was an 87% reduction in hospitalization and an 81% reduction in medical visits as a result of the use of this drug. So these are - this is real option. And we have a lot of experience with remdesivir, particularly those of us on the inpatient side. So I think this biggest hassle is having to come in three days in a row, having to get I.V.s, and having to get to the infusion.

So the NIH recommendations for patients that do not require supplemental oxygen or hospitalization is really to look at the Paxlovid combination therapy as a first line, or remdesivir. Alternative therapies, according to their most recent recommendations, would be to look at the I.V. use of bebtelovimab or the other anti-oral viral agent. Panel recommends against the use of dexamethasone or other systemic corticosteroids in the absence of other indications as an outpatient. And that certainly has not been completely accepted by practitioners, I can tell you from just looking at patients admitted to hospital.

So in summary, monoclonal antibody treatments continue to evolve. And their use has changed over the two and a half years of the pandemic. Their current niche is in the outpatient setting, most likely because of the reproduction - high reproduction of viruses going on at that period. So the earlier they're administered, the most likeliness - the most likely they will be effective. The limitations of monoclonal antibodies for treatment is availability, parenteral administration, and the early course of illness that are required to get them. In light of Omicron BA.2 variants and other variants bebtelovimab is currently the only monoclonal antibody that is authorized to treat COVID-19. Other treatments such as the oral antivirals, Paxlovid, remdesivir, etc., should be considered with very specific review of the patient's medication list and risks and potential benefits. There still is one combination monoclonal antibody that is available on EUA for pre-exposure prophylaxis, and remains sufficiently active against the BA.2 variant and the other variants of Omicron, to be - to show some efficacy.

Although these things are changing on a daily basis, and what we say today, may well be revoked within the next few days.

Thank you very much for listening to this talk. And I would encourage you to go ahead and listen to the other two talks that make up this program on monoclonal antibodies in the treatment of COVID-19. Thank you.

Announcer:
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