FDA experts discuss COVID-19 therapeutic clinical trials

On March 17, 2021 the AMA hosted the sixth webinar in the "COVID-19: What physicians need to know" series.

Hosted by AMA physician leaders, each installment of the COVID-19: What Physicians Need to Know webinar series aims to gain fact-based insights from the nation’s highest-ranking subject matter experts working to protect the health of the public, particularly during the COVID-19 pandemic.

AMA President Susan R. Bailey welcomes three physician leaders from the Food and Drug Administration (FDA) to discuss the state of therapeutic clinical trials worldwide, the challenge of obtaining robust therapeutic data and what the future holds based on current research.

Guests

- Janet Woodcock, MD, acting commissioner, food and drugs, FDA
- John Farley, MD, director, Office of Infectious Diseases, Center for Drug Evaluation and Research, FDA
- Sally Seymour, MD, director of the division of pulmonology, allergy, and critical care, Center for Drug Evaluation and Research, FDA

Transcript

Dr. Bailey: Hello, I'm Dr. Susan Bailey, president of the American Medical Association, and I thank you for joining us today for the latest in our popular "What Physicians Need to Know" webinar series. After a long and difficult year, there is hope that we might be the worst of this pandemic. With the Johnson & Johnson single-dose vaccine authorized for use just days ago and two other vaccines already in wide circulation, there are good reasons to be optimistic, but we can't become complacent or give any ground to this dangerous virus.

Despite vaccine supply shortages and concerning new virus variants, some states have actually begun rolling back masks and physical distancing mandates that are proven to have helped slow the spread of COVID-19. This virus is too dangerous and too unpredictable to act as if we are already

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back to normal. As scientists and physicians, we know that the end of the pandemic, whenever it finally arrives, does not necessarily mean the end of the virus. It may not pose the risk to our daily lives as it has since last year, but COVID-19 and its variants are likely here to stay and because of that, we need to know what to do about them.

Today, we're joined by three leaders from the Food and Drug Administration who are experts in the therapeutics recommended for patients with COVID-19. When this pandemic reached the U.S. a little more than a year ago, there was considerable question among physicians and scientists about how to effectively treat the novel coronavirus. One year later, the data is clear and we have identified a number of safe and effective treatments. From prescribing monoclonal antibodies to using dexamethasone and other solutions in between, today's experts will discuss the state of therapeutic clinical trials, the challenge of obtaining robust therapeutic data, and what the future holds based on current research.

After their presentations, we'll take your questions. Please note that today’s discussion will be limited to therapeutics only. We will not be getting into vaccine allocation and distribution in today's program. That's something we'll get to in another upcoming webinar. Now, without further ado, I am pleased to introduce you to today’s speakers. Dr. Janet Woodcock was named the FDA's acting commissioner of food and drugs in January. She oversees the full breadth of the FDA portfolio, which includes assuring the safety, effectiveness, and security of vaccines and other biological products for human use, medical devices and more. In 2020, Dr. Woodcock lent her experience to Operation Warp Speed, where she specialized in researching therapeutics and treatments for COVID-19 patients.

Dr. John Farley is presently director of the Office of Infections Diseases in the Office of New Drugs at Center for Drug Evaluation and Research at the FDA. His office is responsible for the review of new antiviral and antibacterial drugs. Dr. Sally Seymour is trained in internal medicine, pulmonary and critical care medicine. She has been with the FDA since 2003 and currently serves as the director of the Division of Pulmonology, Allergy, and Critical Care. Dr. Woodcock, I'll hand it over to you to get us started.

Dr. Woodcock: Thank you so much, and thank you for inviting me to participate in this webinar. I'm going to talk about the big picture, and then I think Dr. Farley and Dr. Seymour are going to get into the individual therapeutic, but yes, I went up, as Dr. Bailey said, to HHS and worked as a therapeutics lead for Operation Warp Speed and I learned a great deal about trying to rapidly develop therapeutics, either repurposed drugs or new novel drugs in the middle of a pandemic. If I could have the next slide.

It was really, really challenging and continues to be, although I think it's mitigating a bit. The health care systems were overwhelmed around the world, and so running clinical trials in that setting, we had many health care systems that simply had to stop because they had too many patients to take care of. They couldn't enroll people in trials. We lacked really ready-to-go clinical trial networks that
they could start.

Now, typically for a government-led study, it might take up to 18 months or even longer to get it all organized, get the grants, the trial agreements, all of this stuff organized. We did it in a few months, but still in the middle of a pandemic, that was a long wait time, and so we couldn't leap into clinical trials immediately for substantial trials in the beginning of the pandemic.

The heterogeneous outcomes of this disease were really challenging and the many different scenarios and things that happened to patients. This led to underpowered studies and false conclusions from either observational trials or case series for these small studies, so we were led astray or the field was led astray or misled, I think, by conclusions from studies that just weren't capable of giving answers in this disease.

Even fairly large trials that have been going on over the last few years, and Dr. Farley might talk more about that, or Dr. Seymour, actually have had some conflicting conclusions that I think have to leave clinicians questioning what's the story. For example, the IL-6 inhibitors. Large number of underpowered clinical trials around the world were competing for patients in medical centers, and so we had trouble with enrollment, even though there were tens of thousands of people having the disease in the community, but there was no way to get them enrolled in new trials. Next one.

At the Center for Drugs in the early part of the pandemic, we started to do a clinical trial assessment to help us understand what was going on. Ultimately, we identified over 2,000 trials, almost 3,000 trials worldwide with proposed enrollment in excess of a half a million patients. This was only a third of all the COVID trials that were going on. There were a huge number of observational studies in vaccines and other interventions being studied, but we were looking at the treatment trials that were happening. We saw a steady increase in the number of trials during 2020 and, as I said, the Center for Drugs and my colleagues here were inundated with INDs to study various agents. We saw a shift in the distribution of therapeutic classes during this time. Next slide.

This is just for your reference. If you want to reference the data, this is recently published. Next one. Here's what that expansion of trial landscape looked like over almost a year. You can see that it just steadily rose over time in various product areas. There weren't too many antivirals studied at first, and then it became more common. Similarly, other types of agents increased such as combinations. Next one.
What we decided to do is look at all of these trials and try to assess the robustness, either taking a regulatory action as the FDA, or writing a clinical guideline for practitioners requires solid evidence, robust evidence. How capable were all of these trials that were going on around the world actually giving actionable information? We had to make it more or less arbitrary definitions of what might be actionable because determining if a trial is sufficiently powered to find a treatment effect is not something you would find in the registries, the clintrials.gov or whatever. They'll tell you what their planned enrollment is and what condition they’re studying, but they won't present actual calculations.

We made some simple assumptions to classify the trials whether they were adequately powered and we also decided whether or not they were randomized because particularly in this disease, it appears that I think non-randomized trials are very difficult to interpret. Next one.

We felt we could be criticized, so we did a bunch of power sensitivity analysis looking at, what if we had required more patients? What if we had required many fewer patients? 50% fewer than given the different indications such as hospitalized patients or ventilated patients. How would that affect our conclusions? We found it wouldn't affect it very much and that our conclusions are very robust. This is, again, something you could look at in more detail later if you're interested. Next one.

Here's the bottom line. Of all of the trials that I talked about, the almost 2,900 trials, only 5% met that criteria of being adequately powered and randomized, only 5%. This was true worldwide. It was also true in the United States. Interestingly, if you looked at the master protocols, you can see that they used 26% of the patients, and most of those were the randomized adequately-powered trials because they were actually enrolling a great deal more of the patients than many of these other trials, which in fact were underpowered. Bottom line here, takeaway bottom line, only 5% of all of the trials that were going on in our assessment were randomized and adequately powered to yield actionable information. Next slide.

Theoretically, what would you do in a pandemic to respond efficiently and effectively to a previously unknown disease like COVID-19? Here we had something we didn't know anything about and a lot of work had been done about influenza, but there is a tremendous amount of knowledge about influenza from past experience. This was a totally unknown disease, so really what you want in these circumstance, you want a robust screening mechanism because at first, you're only going to be able to use repurposed drugs.

Why is that? Well, it takes a long time to develop specifically-targeted drugs against a disease. Usually we're talking decades, frankly, so we moved a lot faster this time, but in the beginning especially for treatment purposes, we're talking about repurpose drugs. You want to be able to screen them using both mechanistic hypotheses and any clinical information that you might have from real-world use, say, to guide your prioritization.

Then, and this is what we were lacking, ability to rapidly and efficiently generate definitive highly-
actionable information on safety, efficacy, and who to treat that would be acceptable for review by regulators and also by expert groups. It would go in the guidelines and everybody would know what to do. Both of these mechanisms need to be responsive to emerging information as you learn during a pandemic. We did not have this strong therapeutic trial ecosystem in the United States during this pandemic. Our response looked very, very different. Next one.

We had major gaps in our capabilities. First of all, as I said, the vast majority were not even designed to yield actionable information and weren't capable of it, but we also saw, though, accrual rates in the trials and that also means that even the safety information might not be interpretable with very low accrual to trials. Many of them were noted in the registries as Phase II trials.

In a pandemic, there's not time to do a Phase II trial and then have a long pause and then do a Phase III trial a year later. This just wasn't going to work, but our usual habits translated into what we did during this pandemic. There was significant ... We saw tremendous duplication among the arms. We saw dozens and dozens of trials of hydroxychloroquine, of convalescent plasma, of azithromycin, other type of agencies, all of them small, underpowered. Really probably wouldn't yield information. Next slide.

I think the lesson learned, and I hope we all as a community can take this forward, we really need a broader community clinical trial network. This would have allowed us to respond much more rapidly to the outbreak by enrolling so many more people. We would have been able to enroll people where they live and where they obtain health care through the providers that they trust, but those providers would have had to have the support and some familiarity with running clinical trials and particularly support.

This would enable us to enroll diverse populations. I think everyone was shocked by the disproportionate impact in certain populations in the United States, and yet we had great trouble reaching those. The vaccine trials managed to do that through tremendous effort, and they utilized previous efforts to reach out to the community and get those patients. Frankly, this is the same issue with many chronic diseases and I think we could use a broad clinical trial network in the community to also study those diseases. As I said, master protocols, which are set up, are standing protocols. Generally performed best in the pandemic, gave us the most information. Next one.

What did the U.S. government specifically do? Well, NIH primarily did a lot of trials. DOD did some trials as well. Many were somewhat slow to start up due to the obstacles I pointed out earlier. ACTT, which is a clinical trial network at NIAID, did the definitive remdesivir study and also baricitinib study. It's a serial platform trial or master protocol that is ongoing in studying additional things. INSIGHT is a network that did a trial, hyperimmune globulin. We don't have the readout yet. The hyperimmune globulin actually wasn't ready because it was being diverted to convalescent plasma, which I will talk about in a minute.

Then, the ACTIV trials. ACTIV is a U.S. government industry public-private partnership, but the trials
were all run by the U.S. government and were funded by Operation Warp Speed, of which I was part. This is this whole panoply of trials across the whole scope of types of conditions including, for example, patients discharged from the hospital. There is an anticoagulant study that has started up under ACTIV 4, so a whole range of compounds and COVID conditions were studied in these trials. However, most of them have not had really definitive readouts. We've had about four readouts from the trials, particularly ACTIV 3, the monoclonal antibodies in inpatients.

I think we learned something about the disease because it showed that really by the time you get to be an inpatient, the neutralizing antibodies are not what you need. You have other problems, and so we had three futility readouts there for monoclonal antibodies. The ACTIV 4 and antithrombotics participated with some other trials. Was able to demonstrate that in very ill patients, full anticoagulation is not the best way to go and so forth. These all have been translated into guidelines. Next slide and file for me.

People ask about convalescent plasma and what happened with that. Well, obviously, that's a plausible use for an infectious disease where you don't have any treatment. Everybody knew about that, so there was a very large number of individual emergency requests that came into the Center for Biologics at FDA. Just a huge number and they were being overwhelmed, and so between them and the Mayo Clinic and BARDA, they decided to have an expanded access protocol, but eventually well over a hundred thousand hospitalized patients were treated, and these products were distributed by the blood banks.

The Center for Biologics performed an analysis of low versus high titer outcomes because those were randomly assigned to patients. They didn't titer the plasma so they didn't know whether it was low or high tier, and this suggested a mortality benefit, so that CBER at some point during this issued an Emergency Use Authorization. They've done initial analyses with up to 20,000 treated patients that have corroborated that there is an advantage with convalescent plasma in early hospitalized patients. However, a number of RCTs, including RECOVERY which randomized a very large number of people, have not seen a benefit either in hospitalization or other measures that they looked at.

RECOVERY used high titer plasma based on an available test in Europe. This test isn't all that reliable. It was an antibody type of test and evaluation of neutralizing activity against actual virus is ongoing and we will see a reanalysis based on that when that is done. In summary, there's still a lot of questions over convalescent plasma. A trial was just stopped in emergency departments, which was people are very close to being admitted was stopped for futility recently. The actual best use of convalescent plasma, I think, is still unknown.

With that, the saga of trying to get therapeutics developed in the middle of a pandemic, I will turn it over to Dr. Farley and Dr. Seymour. Back to Dr. Bailey for talking about specific agents. Thank you.

Dr. Bailey: Dr. Farley, go ahead.
Dr. Farley: Great. Thanks very much and thanks very much, Dr. Woodcock. Dr. Seymour and I are going to kind of take you through the spectrum of disease with respect to the therapeutics and the data supporting their use. We'll start with mild to moderate patients where particularly for those who are at high risk for hospitalization, the goal for all of us is to prevent hospitalization and mortality in those patients. Next slide, please.

We'll start with the authorized monoclonal antibodies. Now, neutralizing monoclonal antibodies are designed to block viral attachment and entry into human cells and thus neutralizing the virus. We have three authorized products. We authorized bamlanivimab and ultimately what is now known as REGN-COV or casirivimab and imdevimab administered together in early November. We did that looking at the holidays upcoming and unfortunately our worst fears around those holidays and the subsequent surge came true. We had two independent Phase II studies at the time which suggested strongly that these could have an impact on preventing hospitalizations. We proceeded with that authorization on the basis of those two independent Phase II studies.

We subsequently, of course, committed with the companies at that time to continue to study the product and accrue proper Phase III data. We have now Phase III data for bamlanivimab and etesevimab administered together, which I'll share with you momentarily. Next slide please.

These monoclonal antibodies are authorized for the treatment of mild to moderate COVID-19 in adults and peds patients 12 years of age and older weighing at least 40 kg with positive results of a direct SARS-CoV viral test. Either an RNA PCR or an antigen test in the presence of symptoms and who are at high risk for progressing to severe COVID-19 or hospitalizations. It's not authorized for use in patients who are already hospitalized due to COVID-19.

As Dr. Woodcock mentioned, we've now had a number of futility reads on antibodies in that setting, so we don't have evidence of benefit established. If you wait until late in the course of the hospitalization, for example, if the patient is already mechanically ventilated, we do have at least two trials suggesting that they actually may do more harm than good. Also not authorized in patients requiring oxygen or an increase in their baseline of oxygen due to their COVID-19. Next slide, please.

To define high risk, we did at the time look to the definitions that had been used in the clinical trials in terms of inclusion-exclusion criteria. We know from the field that we would probably benefit by broadening these a bit. We are expecting to do that very soon, but high risk are patients with a high BMI, chronic kidney disease, diabetes, immune-suppressive or receiving an immunosuppressive treatment, or greater than 65 years of age. We've added obstructive pulmonary disease, hypertension, and cardiovascular disease for those 55 and above. Then, we have some risk criteria for adolescents as well. Next slide, please.

There have been a number of trials, and I'm going to take the development of bamlanivimab and etesevimab as an example. We would expect similar data very soon in terms of Phase III data for the
Regeneron product, but that has not yet completed, but we would expect that would occur soon. I'm going to focus in on the Phase III portion of the trial. This enrolled patients with mild to moderate COVID-19 with very high risk of disease progression using the criteria that I just shared with you. Patients were randomized to either bamlanivimab 2800 or with etesevimab 2800 administered together versus a placebo. Next slide, please.

The primary endpoint was the proportion of patients who progressed to require hospitalization or mortality by day 29, and in this Phase III trial there was a 70% reduction in those events. 36 events on placebo or 7% versus 11 events on treatments or 2% with a robust p-value. Of note there were 10 deaths on the placebo arm and no deaths in the treatment arm. People are also looking at persistently high viral load at day seven as a factor that may be predictive and that was predictive in this trial. Next slide, please.

Moving on to hospitalized patients, early on we began trials of remdesivir and, as Dr. Woodcock mentioned, those trials actually began in February, approximately three to four weeks before the U.S. shutdown. We had first patient in a well-powered Regeneron trial of remdesivir that was conducted by the NIH. This is a broadly active antiviral agent. It's an IV formulation. It has subsequently gone on to be FDA approved, so it is an approved drug and it's indicated for adults and pediatric patients 12 years of age and older weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization.

Because of the way the trials were conducted as well as some adverse events that we think are important to monitor for, this drug should only be administered in a hospital or in a health care setting capable of providing acute care comparable to inpatient hospital care. There are a lot of options. There are alternative care sites set up by states and there's also the Medicare waiver for hospitalized care at home program that would be considered an alternate care site similar to a hospital.

There's a single loading dose followed by once daily maintenance dose, and anywhere between a five- to 10-day treatment course is recommended. Of note in the trial is that if a patient reached criteria for hospital discharge, they actually were discontinued from treatment and simply sent home and they did fine. The recidivism rate was very low in the trial. Next slide, please.

As Dr. Woodcock mentioned, this was the ACTT-1 Trial, remdesivir versus placebo, and they used 10 days of treatment in this trial unless the patient was discharged prior to 10 days of treatment. It was hospitalized adults with laboratory-confirmed SARS CoV-2 infection. The primary endpoint was time to recovery within 29 days post randomization. That was defined as either discharged or hospitalized but not requiring supplemental oxygen and actually no longer requiring ongoing medical care.

I have many relatives who worked on the front line and there were lots of patients, as you all know, stuck in a hospital who actually did not require hospital care, so they would have reached the endpoint for this study. It's over a thousand patients, conducted in multiple countries, and you'll notice the enrollment time. This trial fully accrued between February 1st and April 19th of 2020. Next slide,
About 10% of the patients had moderate disease. Most had severe disease and about a third of them were on mechanical ventilation or ECMO. Mentioned the primary endpoint. For the overall results, the median time to recovery was 10 days for the remdesivir group, 15 days for the placebo group for the primary analysis population with a robust p-value. The recovery rate ratio was similar among disease categories and persisted in the severe disease subgroup as well with a rate ratio of 1.31. Next slide, please. I'll turn this over to Dr. Seymour at this point.

**Dr. Seymour:** Thank you, Dr. Farley. I'm going to present a few slides on immunomodulator therapy for COVID-19, so let's start with dexamethasone. Dexamethasone, as you know, is a widely-available corticosteroid. This was studied in the RECOVERY trial. RECOVERY is a multicenter, randomized, standard of care controlled, open-label adaptive platform trial in the United Kingdom. In the trial, enrolled hospitalized patients with SARS-CoV-2. Patients are randomly assigned to different treatment arms, and one of the arms was dexamethasone 6 milligrams once daily up to 10 days.

The primary outcome in recovery is 28-day all-cause mortality. Results with the dexamethasone group have been published in The New England Journal. In total, there are over 4,000 patients assigned to dexamethasone and over 2,000 patients to standard of care control. Results showed a reduction of mortality in patients treated with dexamethasone compared to usual care. The figure I have in this slide is from The New England Journal article and it shows the rate ratio for 28-day all-cause mortality for the overall population is the bottom diamond and the difference of populations that were enrolled.

The absolute reduction in mortality in the overall population was around 3%. Results were most impressive in the mechanical ventilation group with an absolute reduction in mortality of 12%, and patients on oxygen therapy had similar findings to the overall population, a reduction in mortality around 3%. Patients who were not on oxygen did not show a reduction in mortality, and based upon results in recovery the NIH treatment guidelines recommending use of dexamethasone in patients who are on mechanical ventilation, and also in hospitalized patients who are on oxygen. It's not recommended for patients who are hospitalized who are not on oxygen. Next slide, please.

Baricitinib is a Janus kinase or JAK inhibitor. It's approved for patients with rheumatoid arthritis. In November, FDA issued an Emergency Use Authorization for baricitinib in combination with remdesivir. The EUA is for hospitalized patients with COVID-19, two years of age and older, on supplemental oxygen, mechanical ventilation, or ECMO. The EUA was issued based upon the ACTT-2 trial which was sponsored by NIH and this was a large, randomized, double-blind, placebo controlled clinical trial in over a thousand patients hospitalized with COVID-19. Eligible patients were randomized to baricitinib plus remdesivir versus placebo plus remdesivir. The primary endpoint was time to recovery within 29 days.

The results showed that the treatment with baricitinib plus remdesivir reduced the time to recovery by
one day from eight days in patients treated with remdesivir to seven days in patients treated with baricitinib plus remdesivir. Secondary endpoints including the odds of progression to death and mechanical ventilation were supportive as well as improved clinical status at day 29. There were also some numerical trends from mortality benefit.

Based upon the results of the ACTT-2 trial, the FDA issued an Emergency Use Authorization, and the NIH guidelines have included baricitinib and remdesivir for the treatment of COVID-19, but the guidelines recommend it only for use in patients on oxygen, not received corticosteroids. It's important to note that baricitinib does have some safety considerations that practitioners should be aware of, serious infection, blood clots, laboratory abnormalities, allergic reactions, and the FDA has a health care provider sheet that's available for practitioners who are considering use of baricitinib. Next slide, please.

I'm including a slide on tocilizumab because I thought this would be of interest to the audience as there have been new data released in the past few weeks, and the NIH recently released a statement on tocilizumab. Of all of the IL-6 antagonists, we have the most data for this product, and as a reminder, tocilizumab is an IL-6 receptor monoclonal antibody that's approved for a number of rheumatology indications as well as cytokine release syndrome associated with CAR T-cell therapy. There have been several randomized double-blind placebo controlled trials with tocilizumab. I'm not going to go into each in detail, but overall, these trials have had mixed results.

Tocilizumab was also included in the large RECOVERY trial, which I mentioned just a couple of slides ago. This was included as a second randomization in patients who had progressive disease within 21 days of the first randomization. They could be randomized again to tocilizumab or usual care, and recently released results show reduction in all-cause mortality. I have a figure there from the publication frequent with the absolute difference in mortality being 4%.

The NIH issued a statement on tocilizumab with recommendations for its use in certain decompensating patients in combination with dexamethasone. Remember, too, that IL-6 antagonists do have safety concerns with [inaudible 00:36:06] immunosuppression, infection, GI perforations, as well as cytopenias. The package insert for tocilizumab has information on the safety of the product.

This concludes my brief overview of immunomodulative therapy for COVID-19. There are certainly many other products being evaluated in ongoing trials. Hopefully as these trials conclude and readout, results will be promising so that we can add to our treatment parliamentary for COVID-19. Thank you.

Dr. Bailey: Thank you for incredible presentations going over a lot of wonderful data. We have a lot of questions from the audience and we'll take as many questions as we can. The one that seemed to pop up the most and so we'll go ahead and address that one is the use of ivermectin. Evidently, there is a Phase II clinical trial that's due to be completed fairly soon for use in hospitalized patients. Dr. Woodcock, I'm going to throw this one to you. Can you discuss the current evidence base related to
treatment of COVID-19 patients with ivermectin?

**Dr. Woodcock:** Well, I think the basic answer is, again, it's mixed. I saw John nodding. Do you have some more details on this?

**Dr. Farley:** I think it illustrates a lot of the points Dr. Woodcock was making earlier because what we've got is 17 to 20 relatively small clinical trials, many of which have been put together in a well-done meta-analysis. The University of Liverpool is working on this. They've done a great job and they've been outstanding collaborators, but they themselves recognize the limitations. You've got small studies studying different patient populations with different endpoints, and Liverpool is working very hard to avoid publication bias, but you've always got that as a factor. What we're doing is trying to get platform trials going. There is one going in Europe, and then NIH is working with some other partners within the U.S. to get one moving in the U.S. because I think it's an important question that physicians need to answer. I'll stop there and turn it over to Dr. Woodcock.

**Dr. Woodcock:** I would say one of the things I wished in Operation Warp Speed I'd started faster but it was extremely difficult to get going, we're getting going now, is a pragmatic trial of repurposed agents in outpatients because people have a long list. There are people who are proponents of fluvoxamine. There are people who are proponents of ivermectin, cyclosporine. I just saw one today, buproprion, okay? Yes, so what we needed was a very pragmatic trial that everybody would have to keep their mitts off of like a recovery so that it didn't have a hundred different bells and whistles that could be done almost remotely for safe drugs, oral agents so that we could just have something like, does it increase hospitalization? Do a randomized trial pragmatic in that we had so many patients.

No, it was hard to get up and running and we're trying to get up and running now, but I think what John's trying to say, we don't have solid evidence right now. We have hints. We've had hints for a long time on ivermectin, but again, we've had hints on a lot of these agents and many of them have not panned out.

**Dr. Bailey:** Well, and a couple other I've heard of and we had questions submitted about famotidine. about ... cetirizine, H1 and H2 blockers ... Can you give us any information where these are coming from and where they might be going?

**Dr. Woodcock:** Well, early in the disease course, in vitro screens were done and different compounds rose to the top. Hydroxychloroquine, frankly, was a frequent flyer for viral illnesses because it had been tried in a wide variety of... as promising as an oral antiviral. These rose to the top and people started trying them, including famotidine, but one of the things that people didn't look at is pharmacokinetics and the achieved intracellular concentrations of these agents. That turned out to be one of the sticking points for a lot of these. How high do you have to dose these in humans to get to the intracellular concentration that was inhibitory to virus in vitro?

Probably an easier way to get the answer to some of these things would have been to have like
famotidine, okay, a large, pragmatic trial. You could use famotidine, but I think it was tried. A trial was started, but the doses were so high that there were concerns about it trying to achieve the plasma levels that would lead to an inhibitory concentration. That trial I don't think was restarted, so all of these agents that surfaced from in vitro screening and other mechanistic reasoning didn't have a really easy way to get tested.

**Dr. Bailey:** You know, it was so interesting and really kind of disheartening to hear your data about only 5% of the thousands of trial arms that have been executed really generating data that was either randomized and adequately powered. It just seems like such a waste and, of course, you know negative studies aren't a waste. You've got to have negative studies, but [crosstalk 00:42:25] can you get any usable data from the trials that weren't randomized and weren't adequately powered?

**Dr. Woodcock:** Well, as John said, people are trying with ivermectin, but then you run into all of these methodologic problems of, who was randomized? What were the endpoints? How was it done? The convalescent plasma, they're actually doing a meta-analysis on that of RCTs for hospitalized patients because other than recovery, most of them were not large enough. I think at the beginning of this pandemic, we didn't now enough about the disease and its heterogeneity.

For example, monoclonal antibodies, which I was very involved in getting them developed and studied, we took all-comer outpatients and we should have realized that most of the people get better no matter what you do. Treating them with a monoclonal antibody was a dumb idea because it's very hard to treat people. It's expensive and yet they were going to get better on their own and make their own antibodies and they do just fine.

We did very large trials, and yet we only had a very small event rate of hospitalization, and so more trials had to get done and those didn't get into the clinical guidelines and everything until later because of those definitive trials. I think many of the smaller trials were because people naively assumed this was kind of a monotonic disease and we could study like 400 people and that would be really a lot of people to study. That was completely wrong.

**Dr. Bailey:** Continuing on the discussion about monoclonal and polyclonal antibodies, there are definitely barriers to clinical use. There are patients out there that are candidates for these where either through unawareness of that they're available or just the fact that they can't get ahold of them aren't being utilized. How can we overcome the barriers to the clinical use of these therapeutics? The slide that you showed of high-risk groups over 55, over 65, et cetera, when to start, what recommendation do you give clinicians, outpatient physicians like me when to start antibodies in a patient without COVID-19?

**Dr. Woodcock:** Well, I think as early as possible. I mean, that's what we know about infectious diseases and it looks like these will stop the disease progression, but in a nonscientific way looking at the data, I would say it takes a few days, so the people are sick keep being sick for a while. If you treat them early, they're not going to get real sick, but if you treat them right before they're going into a
hospital, they may go in the hospital, maybe they won't go in the ICU.

We had been telling people for six months to stay at home and hide if they were infected, and then the rollout of the monoclonals wasn't the greatest, frankly. It was sent to hospitals on a remdesivir model and the hospitals were in no position to give out monoclonals to outpatients and to ask infected people to all come to our hospital and we'll give you monoclonal. No, that was not going to work. We needed like thousands of small outlets that could manage the PPE, the isolation, and yet could manage the administration.

We're getting there now, but it's taken quite a long time, and then reimbursement is just barely adequate. The ideal, which is the most accepted by patients, is home administration and some large health care systems have done that and we've done some pilots, but to have somebody you know is a high-risk patient, they get an antibody test, I mean, they get a COVID test, you send a team to their home and you give them an infusion. That's a really good... Or in nursing homes where states piloted... They sent outbreak teams in and they could give the whole hall monoclonal antibodies and they really reduced, they think, their hospitalization rate by doing that. It wasn't mass infusion. That mass vaccination is hard enough. Mass infusion was a real challenge for our health care system.

**Dr. Bailey:** Other categories of treatments in early COVID-19 to hopefully prevent hospitalization and then going on to mechanical ventilation and death, antiviral medications, the influenza paradigm where we start antiviral medications for influenza very early on. Later, we realize it doesn't do much good [crosstalk 00:47:38]. What about other antiviral medications that are out there? There's one, molnupivavir. How did I do with that? Piravir.

**Dr. Woodcock:** Right.

**Dr. Bailey:** That supposedly clears SARS-CoV-2 from the nasopharynx within just a few days. What work is being done with other antivirals that could hopefully be given early in the process of the disease?

**Dr. Woodcock:** Well, there are a couple coming along, but I think we all have to realize that small molecules are different than, say, monoclonal antibodies that are directed against a foreign epitope. They have a very good toxicity profile, but small-molecule antiviral drug development is fraught with a lot of safety problems to just be frank.

We're going to have to ... John probably has a better idea about this, but yes, there are new molecular entity, not approved, not repurposed, antivirals under development for SARS-CoV-2. Some are repurposed but were never approved, some are actually specific. Those are earlier, but we have to be realistic. They're going to require more testing before they're ready for prime time I think in general. John?

**Dr. Farley:** I think also it's important to be looking for clinical benefit for the patient, so quantitative
viral load in the nasopharynx. We're still not sure what that means. With the monoclonal antibodies randomized, it was about a half a log difference in the drop, but really the slope of the drop was the same for the high-risk patients who ended up in the hospital versus those who don't. There are a few that had a sustained high-viral load, but we don't know yet what the clinical benefit is. I think for the agents that are outpatients, I'm sure, Susan, you would be looking for us to show you evidence that we could keep your patient out of the hospital if they were high-risk.

I think there are companies interested in showing symptom improvement faster, and I think that that's possible. They're working on that. We're working on the tools to measure that acceptably, so then you'd have drugs kind of similar to Tamiflu for COVID, but I think we're all looking to keep our highest risk patients out of the hospital right now and hopefully we're getting those high-risk patients vaccinated as quickly as possible.

**Dr. Bailey:** Oh, amen to that. Dr. Seymour, talking about IL-6 receptor inhibitors, the tocilizumab data is at least partially to me a bit concerning because of these people are often so incredibly ill and have their own issues with various thrombocytopenia and other things. Just from the viral disease, I would think it would be very difficult to separate out what disgraces you're seeing or result of the medication or result of the disease itself. Are there other IL-6 inhibitors that are being looked at?

**Dr. Seymour:** Before we answer that question, just a note about the safety profile. I mean, what we know about the safety of the IL-6 inhibitors is based upon their current clinical use, which is more of a chronic use, and so the use for COVID-19 is shorter duration, a single dose in some cases. Those safety concerns, I think, need to be taken into context with the duration of use here.

There are other IL-6 inhibitors that have been studied. Sarilumab had a study early on in the pandemic that didn't show a benefit. Very different time in this past year, and there has been some data with siltuximab, another IL-6 antagonist. Again, very limited data, so really the body of data that we have is primarily with tocilizumab and it is a little bit all over the place with some of their randomized controlled trials. The biggest amount of data we have is from recovery.

**Dr. Bailey:** Dr. Seymour, I'm going to stay with you here and talking about steroid therapy. At what point, where's the time where you should add steroids? We know that if you add them too soon, that's not great. If you wait too long, that's not great. What are the signs that the patient is transitioning from the viremic stage to the inflammatory stage? Is it when they become hypoxic? Is it when they need hospitalization? What are some good time points?
Dr. Seymour: It’s definitely not a therapy that you would use on an outpatient. Dexamethasone really shouldn’t be routinely be used in outpatients. I think for our patients who are hospitalized who are fairly stable and are not requiring oxygen therapy, again, in the RECOVERY trial, those patients didn't show a mortality benefit, so I wouldn’t necessarily use them in those patients, either. If your patients are showing signs of deterioration requiring oxygenation, I would definitely be adding dexamethasone onboard for them right away.

Dr. Bailey: Right. As far as the variants, the new COVID-19 variants that we’re hearing more about every day, and I’m going to open this up to all three of you, do we have any knowledge about differential therapeutic benefits in the different variants of the COVID-19 virus?

Dr. Woodcock: Well, I will say as part of Warp Speed set up with FDA and NIH and BARDA, we set up a pseudovirus assay, and so we have done this in hundreds of variants and we’re able to pretty rapidly screen the monoclonals against the variants. We just have to make sure the company will give us their monoclonals because there are a lot of monoclonals out there. We do have a lot of knowledge and seems to be pretty predictive, so John?

Dr. Farley: Sure. I think starting with two pieces of good news, relatively. You have the UK origin lineage variant that's becoming highly prevalent in the United States. Fortunately, from some of those assays as well as other data that Dr. Woodcock mentioned, we're confident that the three monoclonals that we have authorized will remain active against that variant. We do have other more worrisome variants with substitutions that are quite concerning and ... FDA and CDC are working together to provide more up-to-date information for physicians on those, and so you should see that shortly, both in the fact sheets that we provide for an Emergency Use Authorization. Give you the most up-to-date virology information we have and CDC to provide the most up-to-date prevalence information for your state that they have.

Dr. Woodcock: Yeah, so the folks who are distributing the monoclonals for the U.S. government are not distributing bamlanivimab into the Southern California, Arizona, Nevada area because of the prevalence of a certain variant there that does not seem to be very susceptible to bamlanivimab alone.

Dr. Bailey: Okay, that's important information. What about antithrombotic therapies? I think there's been a lot of ebb and flow of the popularity of the use of antithrombotics in COVID-19. Where are we with that?

Dr. Woodcock: Well, the ACTIV-4 study is studying that and they’re actually studying outpatients and looking at antiplatelet agents. They're looking at inpatients, and that's where I said they have read out the very severe patients. They found that full anticoagulation, if I’m remembering this correctly, is not good, that they should have a fractionated heparin, and oddly enough, they found that in the less severe patients, they do better with fully anticoagulation...
Dr. Bailey: Okay.

Dr. Woodcock: ... and then, they are studying discharged patients and they've been enrolling people with discharged patients with oral anticoagulants to see if they can... That's not a very high rate of thrombotic complications after you're discharged from the hospital. That is not negligible, and so they're seeing if a smaller intervention could potentially decrease that. Then, they've started looking at adding things to their baseline regimen now of in-hospital anticoagulation, so they've started additional arms. That trial seems to be enrolling pretty well and it's putting out information, so that's the state that we're in right now.

Dr. Bailey: Great, and I'm going to kind of wrap things up here before we conclude. Dr. Woodcock, you talked about the research ecosystem and, of course, the COVID pandemic has revolutionized the ecosystem just in terms of the pace of the generation of evidence, data and resource sharing, novel analysis, diverse sources of information to guide public health decision-making. In the future, it seems like we've got a great opportunity to proactively reform, create a research ecosystem in the new environment. Is the FDA planning on working on this proactively?

Dr. Woodcock: Well, I certainly am, and I'm going around advocating for it because we have to look at our performance and what we could have done and look at places like the UK that mounted the RECOVERY trial that has yielded really tremendous information. I think there's several factors. One is if we can get to the point where we can run an investigation primarily off the health record, we're going to be in a lot better shape, and so some of those pragmatic experiments, hopefully we can do that.

Number two, if we can get support out in the community and set up more community-based research so that it isn't just the province of the big medical centers, it’s where the people live and get their health care. Then, number three, I think we're going to do lessons learned about this and some of it will be about, "Okay, how do we have a little bit more planning, shall we say?" Overall planning and really plan to generate evidence quickly because it turns out we have the capability, we simply didn't have the structure. We didn't have the structure to conduct these large trials and try to chivvy everybody into participating in a larger trial rather than having their own trials.

Dr. Bailey: Great. Well, thanks so much to our audience for joining us and for all of these great questions. We've learned an awful lot today. I know I have. We've learned about therapeutics that are actually available for younger patients, up from age two and up. We've heard about the importance of using antibody cocktails or single-antibody agents as outpatients hope to prevent hospitalization, saving dexamethasone until a patient becomes hypoxic, and then other more aggressive therapies as indicated once the patient is hospitalized.

We will be in touch with the date and the time of our next webinar very soon. If you're interested in sending this webinar to a friend or watching past episodes, this What Physicians Need to Know web

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