Ruth Adewuya, MD:

Hello, you're listening to Stanford Medcast. Stanford CME podcast where we bring you insights from the world's leading physicians and scientists. If you're new here, consider subscribing to listen to more free episodes coming your way. I am your host, Dr. Ruth Adewuya. Thanks for tuning in. This episode is part of the COVID-19 mini series addressing up-to-date insights on COVID-19. In today's conversation, I'm joined by Dr. Anne Liu. Dr. Anne Liu is a specialist in allergy immunology and infectious diseases and is a clinical associate professor of pediatrics and medicine at Stanford university. Thanks for chatting with me today Anne.

Anne Yee Liu, MD:

My pleasure. Thank you so much for inviting me to speak and I look forward to our discussion Ruth.

Ruth Adewuya, MD:

So today we are discussing a highly complex topic and I know that we cannot cover all things immuno modulators and COVID in the time we have. But I'm very pleased to have you here to share some of your insights on this topic area. So, I thought a great place for us to start, would be for you to help set the stage for our discussion. Can you provide a high level overview of immunology as it relates to you our discussion today?

Anne Yee Liu, MD:

Term in immunology, as anybody who has studied the immune system can tell you. Is an incredibly intricate and complex system with lots of redundancies and feedback loops and internal account or regulation. There's often that study that will say the opposite of the study that you're looking at. We'll say under certain controlled conditions and usually that's cells in a dish or mice with a certain phenotype. And so it can be really hard to sort out. So, I'll try to talk about what we generally think is going on, knowing that there's going to be a lot out there that is contradictory and especially at this stage of our understanding of COVID. So, when we think of inflammation, sometimes there's an implied dichotomy of too much or too little with inflammation measured on just a single axis. In fact, the immune system can deploy many different types of inflammation that can produce a lot of different outcomes when acting alone or in combination. For respiratory viral infections, including Influenza other corona viruses, her influenza viruses.

And the viruses things that are common. We need the immune system to turn on certain pathways to effectively control the virus. But unchecked activation of the same pathways can then harm the host. That is the infected person. In addition, the activation of other pathways can be helpful if they're finely tuned. They can also lead to broad destruction in death. Some viral infections become lethal because of the inflammatory response that is triggered by the virus. But then continues even after the virus seems to have been brought under control. So, medicine has a very long history of using immunosuppressants to try to affect the immune system, to reduce the inflammation during infections. But in respiratory viral infections, I would say that the results have probably been more failures than successes. And the timing of these responses probably is key to whether they're helpful or harmful. And a pathway that's helpful early on could be harmful if it's triggered or active late in the infection.

And in COVID, one of the early observations about the immunologic response in COVID came from critically ill patients. Who exhibited impressively high levels of inflammation. And mortality was higher in these hospitalized patients who've had really high levels of markers of inflammation, including C-reactive protein and interleukin six or IL-6. And the medical community really quickly went for

therapies to dampen the immune system. But now it's actually not surprisingly turning out to be much more complicated than that.

Ruth Adewuya, MD:

When it comes to COVID, how do we think this early response is taking place?

Anne Yee Liu, MD:

Well, it seems to be key in the early response in COVID is production of a group of molecules called Interferon's. Their production is triggered by innate viral sensors, upon viral entry into cells via the ACE two receptors. There are several classes of interferon's type one and type three interferon's that are the most relevant to respiratory viral infections. And type one interferon's drive antiviral responses through activation of other pathways up regulating transcription of other cytokines, stimulating anti-viral activity of effector cells to eliminate the virus. And promoting antibody generation and memory formation. And the antibody generation is a hot topic because it's something that's easily measurable to see if somebody has been infected. And that's just one of the outcomes of this response.

Ruth Adewuya, MD:

You mentioned that the early response around COVID has to do with interferon's. And so, what are your thoughts around if they are produced early? What are the implications of that for an infection?

Anne Yee Liu, MD:

We think that early production of interferon's, as soon as the virus enters the host, maybe needed to get control of the virus to reduce rival replication and prevent future subsequent damage to tissue. If the interferon response doesn't happen early it's possible that viral replication gets to a point where then it becomes hard to control. And not only are the interferon's turned on, a whole host of other inflammatory responses are turned on.

This is somewhat of an over-simplification, but there have been studies showing that people who have more severe disease and bad outcome seem to have an impaired interferon response especially early on. And they seem to have much more non interferon type inflammation including production of IL six and TNF alpha or just Tumor Necrosis Factor alpha, another pro-inflammatory side effects. And a whole host of other inflammatory signals. So, we think that, if you can produce an interferon response early on and then get control of the virus and then shut it off, shut off the virus and the interferon response, then the host may have a mild or asymptomatic disease.

If the interferon response is not turned on early, then viral replication happens and it starts to damage tissues, spreads in the body and may lead to then a widespread inflammatory response that is more nonspecific. Which also includes interferon but a whole host of other inflammatory cytokines. There have been also a number of reports on how the virus itself is uniquely adapted to suppress the interferon response. And this is research that extends from the first SARS virus and the MERS, the Middle Eastern Respiratory Syndrome. And those viruses have also been shown to impair the host interferon response to some degree. And this virus, SARS COVID two virus has quite a number of adaptations that suppress the host interferon response.

It really triggers multiple mechanisms to evade host detection by preventing interferon production. And that may be one reason that people don't have symptoms even as the virus is taking hold and replicating because of these evasion mechanisms. And then things can go downhill after the virus has had a chance to replicate.

Ruth Adewuya, MD:

So, is this where the concept of immuno modulators as a mechanism to treat COVID comes in? If so, can you talk about what are immuno modulators? And then we can dive into the different types.

Anne Yee Liu, MD:

In this context, immuno modulators are potential therapeutics that work by modifying the host immune response. In contrast to medications that target the virus itself. So, the thought of using immuno modulators comes from the concern that this unchecked inflammation, especially later in disease, is what is causing the damage, causing all the problems as opposed to the virus replicating itself.

It is also in the context of thinking once the virus gets going, we need something to dampen the immune system as well as act on the virus itself. So, the group of medications that target the virus itself include things like Remdesivir, possibly lopinavir/ Ritonavir, or at least people have looked at it for that. So, Avifavir in Monoclonal antibodies that target the spike protein or other components of the SARS COVID two virus itself. Convalescent plasma probably falls in this category since we speculate that the mechanism of action is binding the virus directly.

Immuno modulators though target the human immune system to either augment or impair some function of how the human body responds to infection or inflammation. The first group, those that augment the human immune system include things like interferon that we can actually administer as medications. Intended to assist with the endogenous in it anti-viral immunity with a boost of these anti-viral cytokines. Which could be particularly important when dealing with a virus that has specific mechanisms to disable the endogenous interferon pathway to the detection. But again, the timing may turn out to be really critical as to when these interferon's are administered. And then the second group, those that impair some function of how the human body responds to infection or inflammation are a much larger group of agents that suppress some pathway in the immune response. And some of these may prove to be useful for the later stage of COVID.

We are, I think, cautious about using them early in COVID because of the possible impairment of an antiviral response. But they may have some applications when used for the broad non-specific inflammation that drives organ damage. Most of these were not developed to treat viral infections. And in fact, they were developed to treat diseases where the immune system becomes over reactive or abnormally reactive, like rheumatoid arthritis, other autoimmune conditions, or auto inflammatory disorders like gout. Or diseases where some component of the immune system proliferates abnormally, like some types of lymphoma. Or they've worked like broad immunosuppressive, like corticosteroids which hit the immune system a whole bunch of different pathways.

And publicly and privately funded research have invested really heavily over the years in the development of these drugs for chronic conditions. And the amount of investment in these drugs has completely dwarfed any investment that has been made into the development of antiviral medications outside of HIV and Hep C drugs. And as a result, our tools of medications that we have on hand that are already at FDA approved for some of the patients is heavily weighted towards immuno suppressive as opposed to potentially effective antivirals. And so, I think that that is part of the reason that they are being used in why you know, trials of [inaudible 00:11:45] agents have proliferated in the way that they have.

Ruth Adewuya, MD:

Let's drive into the conversation of this immuno moderators. My understanding is that there are several of them that are currently under evaluation for use and COVID-19. And just listing it off from reading I

see the interferon's, you mentioned interferon, you mentioned corticosteroids and maybe we can talk about anti IL one, anti IL six and kinase inhibitors from your perspective, are those the general buckets of immuno modulators that are currently under evaluation?

Anne Yee Liu, MD:

Yeah. I would say that covers it as far as the medications that are immune boosting, it's mostly the interferon. There have been a couple small randomized trials thus far on different interferon's. And in a press release interferon Alpha is FDA approved for use in hepatitis B and a variety of other virus driven diseases, including Condyloma acuminatum which, is caused by human papillomavirus. Kaposi sarcoma driven by human herpes virus, eight HHV eight. And we used to use interferon alpha also for Hep-C. Now Hep-C hepatitis C treatments have completely changed. And if you're on Beta is also an FDA approved drug with anti-inflammatory effects and it's approved for use in multiple sclerosis. And then there's an investigational agent including interferon Lambda and Kappa. Interferon Lambda is a type three interferon. It seems to have protein antiviral effect without driving inflammation as much as the type one interferon. Is sort of slow to turn on and slow to turn off and type one interferon.

And it's being studied for use in COVID as well as in viral hepatitis. So, the interferon's are a pretty fascinating group of potential therapeutics in COVID. A couple of studies, one from Hong Kong, a couple from Iran, and then another one from the UK looked at interferon beta. Three of those were subcutaneous interferon beta one was inhaled interferon beta. And I think a couple were open-label and one of them, the inhaled interferon beta was placebo controlled, double blinded trial. And, as a whole, they did suggest that interferon beta, given early on might have benefit in COVID. The inhaled interferon beta study we know about from press release only I have not seen a pre-print of the data itself. And this is a unique feature of how we're operating in a COVID world. And you're making lots of decisions by press release without the whole data.

Ruth Adewuya, MD:

I was actually going to ask you about that, because I think you mentioned that earlier kind of by press release. So let's talk about this new reality. It sounds to me that we're all getting some information around these studies from press release. How has that impacted how you look at the data and how you do work?

Anne Yee Liu, MD:

For the drugs, for which there is no FDA approval and it's being trialed in this setting. It may not change things that much because if it's not available outside the clinical trials. Then we still have to wait for the data. We still have to wait for approvals and so on. It changes things in become sort of controversial how to deal with it in situations where the drug is FDA approved for something else. So, it's on the shelf we have it readily available and we get a press release that says that, these people did a trial and it looked like it was helpful and we have very little other data. And then the COVID patient now, who might fit that inclusion criteria but we don't really know much more about it. And we're just used to being able to dissect the data before we really have a change in our practice.

And that I think that there is no right answer. I've seen from my colleagues who all very smart people, some of whom say, we need to still wait for the full data before we change anything about our practice. We can't do anything differently for this patient right now, or the patient who comes after the patient until we have the full data. And that's our responsibility to the patients. And others say, we have to do something right now. We know that in some context we don't know all the details. In some context, this drug has been helpful for patients with this disease. And here's a sick patient in front of us.

We have enough justification to use this drug and lots of other people in between. There's no, I think right answer. And, I have seen at least one instance where a press release that 8:00 AM changed management by noon that day, even with all the full data.

And this is an uncomfortable space for most of us, especially infectious diseases, doctors who love to gather all the data and sift through everything before making a decision. I hope that the information keeps coming. You know, certainly it's not that we don't want all this information and we don't want the press releases and that we want to wait for the full data on everything we do want to know about it. But it does create a tension I think, within ourselves that how quickly do we change our practice based on this information. I think we wind up having these discussions of risk benefit. So, is this a therapy that has potential downsides and how big are the potential downsides? Based on the mechanism that we understand, does it make sense to use this drug in this context? Is it an incredibly expensive medication with a limited supply or is it something that is widely available and quite inexpensive?

Quite a number of these immuno modulators are very expensive. There are some that are in clinical trials that are at the approved for something else that are in the range of $20,000 per dose. And I think that we have to have some pretty solid justification to pull out a medication like that, especially since immuno suppressive also expose patients to risk of infection. And they already have an infection. So, I think that we need to have pretty solid ground to stand on before we layer on something that will impair their immune system. We have seen from some of these studies of immunosuppressive, that there is probably some increased risk of bacterial infections, so bacterial pneumonia and in some cases, fungal infections, fungal pneumonia. So we could also be doing more harm than good. Dexamethasone, turned out that in a large study that and in this arm, they enrolled a thousand patients in the UK, in the recovery trial. There was a mortality benefit that was primarily seen in severe and critically ill COVID patients.

It didn't seem to have that effect in patients with moderate disease. And in fact, there was actually a trend toward possible worst outcomes when it was used in patients with moderate disease. And so this goes to the importance of what stage are you using these immuno modulators, how you need to pick your patient population very carefully. And there have been other studies also looking at steroid use in COVID some of which have been positive studies and some have been negative. So, it's not an entirely clear benefit that you get from steroids. But there was enough in this study that shows that a six milligrams daily of dexamethasone reduced mortality at 28 days out versus usual care. And with the greatest difference in patients who are on mechanical ventilation. And this is great news because at the time people were studying and continue to study all kinds of really expensive immuno modulators. And most of which would be out of the reach of COVID patients and most of the world.

And it was great news that dexamethasone, could be an effective immuno modulator because it's inexpensive. It's widely available globally. It's a few dollars per there appear and hopefully even less expensive in resource limited setting. And it gives us a treatment option in later and more severe disease. Extrapolating from the antiviral treatments in general early treatments before severe disease seems to be the best window for giving antiviral. So, drugs are directed against the virus. And I think in general, we're expecting that will probably be the case for various anti-viral therapies, including Remdesivir, Convalescent plasma and antibody therapies.

Then there's evidence of severe inflammation then it may be too late for some of those antivirals. And it may be risky to be giving interferon that boost immune response. So, that steroids can probably help the patients who benefit less from antiviral therapies. And in human would have the concerns about using interferon's is great. And it also underscores that there's probably different stages of the disease that steroids are probably helpful in severe and critical illness and potentially harmful in

moderate disease. Because the recommendation currently is that it should be used in patients requiring supplemental oxygen.

Ruth Adewuya, MD:

The other group of drugs that I wanted to talk to you about are the kinase inhibitors. And I wanted to ask you from your insight, what is the rationale behind the use of kinase inhibitors for the treatment or for use in patients with COVID-19?

Anne Yee Liu, MD:

It is another group of immuno modulator. They are thought to be safer than some groups of immunosuppressive because the risk of infection may not be quite as high. They also don't last as long in the system, they're all we administer. And I think we're talking about the JAK inhibitors, the Janus kinase inhibitor. They work by inhibiting Janice kinase and Janice kinase functions by activating cytokine receptors and generally promoting inflammation. And so, there are another group of anti-inflammatories. It's concerning that and a number of experts has read in the beginning that they can also inhibit the production of type one interferon. And so they may actually inhibit viral clearance. There is a known increase risk of herpes zoster from the varicella virus and HSE or for B simplex virus. They also can impair lymphocyte proliferation and cause neutrophil counts to go down. So there've been concerns from the beginning about whether they would be helpful or harmful.

Again, it will probably turn out to be a matter of the stage at which they're used. One of them very sitting there was then studied in act two. Act two is the NIH funded, adaptive clinical trial for COVID that looks at one therapy then, once they finish that study, they then enroll for another therapeutic and so on. So it's no Larry therapeutics one on top of another. And act one was on Remdesivir versus placebo. And once we saw that there wasn't effective act two was Remdesivir versus Bersin as class Remdesivir. And there was a press release, of course, just last week. I think it was on September 14, in which they announced the top-line results. And actually it was a manufacturer of Bersin of that releases information. And as far as I can tell, I haven't seen much from the NIH itself about the results of this study.

And the only thing we know is that it met the primary endpoint of reducing times recovery in hospitalized patients by one day. And there were a thousand patients enrolled. And it also met a key secondary end point of day 15 clinical outcomes and that's pretty much all we know so far. So yeah. Then the question is a one day difference. Yes, it's statistically significant. Is it clinically significant? Is it enough that it would change our practices? Especially since and this goes for all the medical classes. Now, that dexamethasone is pretty much standard of care in patients needing supplemental oxygen and dexamethasone and all corticosteroids are already immune suppressants. Do we want to layer on another immunosuppressive when the benefit may be sort of marginal? But it may significantly increase the risk of infection? We don't know. We're concerned that Larry needs new suppresses on each other would increase the risk infections.

Ruth Adewuya, MD:

I wanted to ask you about interleukin six inhibitors. And I know that there are and correct me if I'm wrong. There are two classes of FDA approved ones right now there's the anti IL six monoclonal antibodies. And then there's the anti IL six receptor monoclonal antibodies. Is that correct? And are these classes of drugs also being evaluated for COVID? And if so, can you talk about what's the rationale behind it and what kind of data do we have on it's used for patients with COVID.

Anne Yee Liu, MD:

The anti IL six medications were used initially just off label people trying them out because there were these patients in front of them who had evidence of really market inflammation. In some settings, in some countries you can measure the IL six levels very quickly and easily here we tend not to do that as much as we do see reactive protein, which is downstream of IL six associate PRP turns out to be a pretty good marker of biophysics activity. And, in some studies they reported that IL six levels when really high were predictive of bad outcomes of mortality. But in some of these studies, IL six was the only cytokine they reported. And when others looked at, other inflammatory cytokines, they found that also IL one was up, sigma alpha was up a whole bunch of other inflammatory cytokines were up. And so it wasn't just an IL six story.

But nevertheless IL six is elevated in many of these patients and does seem to be associated with, or seem to be a predictor of bad outcome. What has been sort of our current scene from some of these immunosuppressive modulator medications is that, they seem to sort of shut down the fever, they may reduce the inflammation, but they don't necessarily improve overall outcomes. And so, are they just putting out some of the flames of the manifestation of the infection without actually changing the course of the infection itself? So, these will possibly answered over time.

Ruth Adewuya, MD:

There's tremendous research and the tremendous work going into understanding all of this, but also the complexity of not having all of the data as you mentioned. And how does it impact clinical practice. The last group that I wanted maybe for you to touch on is the IL one inhibitors and curious to see what your insights are on the use of IL one inhibitors in COVID?

Anne Yee Liu, MD:

The IL one inhibitor have been looked at also because of this thought that there is a cytokine storm going on in these patients. There are signs of who have looked at and compared the level of cytokines. So, IL six, TNF, IL one among different conditions, including Andia and sepsis and cytokines produced in other respiratory viral pneumonia, including influenza. And I've found actually that in COVID the level of cytokine production is not as high as in some of these other conditions. So, perhaps it's I wouldn't say inaccurate, but overly broad term to say that there is a cytokine storm going on. So, that said people are also trying other FDA approved agents like the anti IL one agent. Because again, they're in our tool box, we have them on the shelf. You know, people said this patient's really sick. Let's try it out. There have been retrospective cohort studies perspective cohort studies, but we still have very little data on how these agents would go in COVID. In the case of something like dexamethasone or corticosteroids that I'm sure we will talk about it.

Ruth Adewuya, MD:

Yeah. Let's jump into that. Yeah. I think that's the second bucket corticosteroids. I know that there are some guidelines right now with the CDC, I think, around the use of dexamethasone. So how are we using it right now for COVID?

Anne Yee Liu, MD:

I think that the dexamethasone data makes the bar for any other immunosuppressive quite high. You have to really justify not only the cost of these medications compared to dexamethasone which is very

inexpensive. But also the risk of adding infection, whisk in a patient who's already in front of us because of an infection.

Ruth Adewuya, MD:

Thank you so much for sharing those insights with us and sharing kind of what's in the toolbox right now around immuno modulators. So Anne, any thoughts on the future direction of immuno modulators in COVID? Just as we wrap up our conversation.

Anne Yee Liu, MD:

I think that there is a lot of enthusiasm on early use of interferon in various forms. There is some enthusiasm about the new cobol application by spray or inhalation of interferon's to boost the anti-viral response. And I think that there was enthusiasm to use these in combination with antivirals. I think that we will be using the immunosuppressive more in later critically ill disease and using it very sparingly if at all in early disease. So, hopefully we can come up with regimens for each stage of disease and also come up with biomarkers to tell us what stage of the disease somebody is in, in addition to just their clinical parameters.

Ruth Adewuya, MD:

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