Jeffery Strich, M.D.

Behind the Mask Interview

October 15, 2020

Barr: Good afternoon. I'm Gabrielle Barr of the Office of NIH History and Stetten Museum. It's October 15, 2020 and I have the opportunity to talk to Dr. Jeffrey Strich. Dr. Strich is a staff clinician at the Critical Care Medicine Department at NIH's Clinical Center. Thank you very much for being with us. We have several questions because you have been very, very involved in a lot of COVID-19 research and care and very interesting experiences. Our first question is: Can you elaborate about your study that appeared in Lancet Infectious Diseases that looks at the mounting need to develop new antibiotics to treat drug resistant infections and discuss how your research has affected the way physicians across the country have approached caring for coronavirus cases.

Strich: Yes. And first of all, thank you for the opportunity to speak with you today. Prior to COVID-19 my interest evolved around the treatment, epidemiology, and development of new antibiotics for highly resistant gram-negative infections. We were working on a study to evaluate what the market size looked like for future antibiotics. One big problem in the space of antibiotics is that there's a significant number of patients who die each year from antibiotic resistant infections and the antibiotics development space is lagging behind in its abilities to develop new antibiotics for the future.

The goal of that study you're referring to was to evaluate how many treatment opportunities there are for patients who have highly resistant gram-negative infections and to quantify that as it relates to development of new antibiotics. What we found was that overall there's a low number of antibiotic resistant infections out there which is part of the reason why antibiotic and pharmaceutical companies aren't particularly interested in developing new antibiotics because there is not a strong market for their future use down the road. What we concluded from this study again is that the market size is small.

I think that one of the take-home messages between what's going on right now with COVID-19 and the realm of antibiotic development is really one of preparedness—national security—being ready for future infections. If we do not continue to develop new antibiotics, there could be a time when the number of infections continues to increase and we see ourselves in a scenario [such as] we are today with ineffective therapies and rushing to do big clinical trials in the middle of a pandemic. The ACTT (Adaptive COVID-19 Treatment Trial) studies are a group of studies that intramural investigators at the NIH enrolled patients in during the initial surges of pandemic in an attempt to find effective therapies. It's very, very difficult. What we don't want to do is let our antibiotic development lag behind and then be not prepared when these numbers of infections persistently increase over time.

Barr: Definitely. Currently you're involved in another study which is sponsored by the [National] Heart, Lung, and Blood Institute in collaboration with INOVA Health Systems that's evaluating the safety of fostamatinib —I don't know if I am saying that correctly—in comparison to a placebo and how to assess the disease progression in COVID-19 patients. First, can you define "fostamatinib" for those of us without a scientific background and why that is so important in treating and preventing conditions in COVID-19 patients?

Strich: That's a great question. The drug is called fostamatinib. It's a spleen tyrosine kinase inhibitor that we hope can dampen the immune response that patients develop that lead to some of the clinical outcomes that we see in patients with COVID-19.

Where we are today in the world of COVID-19 is we know that remdesivir, the antiviral that was studied, decreases time in the hospital from 15 to 11 days. That was studied in the ACTT-1 study but that targets the virus. In addition to the virus, what needs to be treated is the patient's dysregulated immune response to the virus. For that right now, there's been a large study from the UK which showed that dexamethasone, a broadly acting steroid had some ability to improve outcomes by decreasing the inflammation, but there's concerns with just using dexamethasone in terms of side effects. Does it lead to prolonged viral shedding? It doesn't have a targeted focused mechanism of action. Patients can often become delirious or hyperglycemic. There are all sorts of different side effects and subsequent infections that may occur with dexamethasone. So, what we're targeting, and hoping to find with Fostamatinib, is that it is a targeted immunomodulator that can influence the host response to the infection and ultimately improve patient outcomes in that way.

So, in addition to the antivirals which target the virus, we want to target the host immune response in a very targeted way.

Barr: Interesting. What was your inspiration for this study? Has this idea of how it works been used in other diseases?

Strich: Fostamatinib is currently FDA approved for a condition called Chronic Immune Thrombocytopenia which happens in patients who develop low platelet counts. One thing that we think fostamatinib can do, and why we are so excited about it, is that it works on three different cell types or three main different cell types that are all involved with some of the pathogenesis of COVID-19. This includes monocytes and macrophages which lead to the increased cytokine production that these

patients have. It also works on platelets which when activated lead to immunothrombosis or small blood clots. As people are aware, patients with COVID-19 are at increased risk for blood clots and have a hypercoagulable state.

But the thing that really has us excited about this drug, and some in vitro data we have, is that this Fostamatinib also works on neutrophils. The concern with neutrophils is that when neutrophils become activated, presumably by antigen-antibody complexes, they release something called NETs, neutrophil extracellular traps, and that extracellular DNA binds to different proteins and acts essentially as a web-like structure to capture bacteria and viruses that are in the blood. Those neutrophil extracellular traps, the NETs, also drive this immunothrombosis leading to, neutrophil platelet aggregates, and can drive some of the blood clotting that we're seeing in these patients at the macro and microvascular level.

So, we think that this drug has a targeted mechanism of action across those three main cell types that are all involved with COVID-19 and then we can hopefully decrease the cytokine response, the dysregulated immune response, and also the immunothrombosis by decreasing platelet aggregation and release of neutrophil extracellular traps, or NETs.

Barr: Interesting. How is your study structured and how many people are slated to be part of the trials?

Strich: Great question. This is a multicenter study between us at the NIH Clinical Center, where we are actively recruiting patients to come from any local hospital in the geographic region, but it's also in collaboration with INOVA Health Systems and, in particular, the Inova Fairfax Hospital. So, there's two main sites. The goal is to get 60 patients into the study in a placebo-controlled randomization where 30 patients get the drug and 30 patients get placebo. Our primary outcomes is safety and then we evaluate some clinically relevant efficacy outcomes.

Barr: How are you involved in the daily aspects of running this study?

Strich: I'm the Principal Investigator for the entire study. I'm overseeing all the patients that we recruit here to the Clinical Center. I'm in constant communication with multiple different hospitals in the local area to see if they have patients who can come over and would benefit from care at the NIH and

enrollment in our trial. I'm also overseeing the study at INOVA. I'm not involved with the daily care of the patients at INOVA. There's a site team that's running the trial there, but I'm helping coordinate to make sure that things that are being done at the NIH the same as INOVA and helping to enroll the patients.

Ultimately, when patients are discharged from INOVA, they're actually coming back to the NIH Clinical Center for the outpatient phase of the study. I'll be leading the clinical care of the patients after they're discharged. While we have a great Critical Care Medicine Department here at the NIH who's helping to care for the patients, I'm also a part of that team that will care for the patients who are admitted at the NIH Clinical Center.

Barr: What challenges have you had in getting this study running? How has this experience differed from maybe past studies that you have been a part of?

Strich: There's two big challenges with this study as I see it. They're different at INOVA than they are here at NIH. At the NIH the hardest part is finding patients. We don't have an emergency room. There's not a lot of patients with COVID-19 that are chronically cared for here at the NIH. It's setting up a network of other hospitals and collaborators who are willing to transfer patients who would ultimately benefit by being here at the NIH by potentially getting a study drug and being part of our study. The advantage of being here is that we can do a lot of in vitro correlative science for these patients and for this study to really help define the mechanism of the action of why we think fostamatinib is going to work.

The INOVA challenge is a little bit different. They have more patients than we have for obvious reasons. They have an emergency room. Patients are just coming in, walking in, off the streets. They have greater access to patients. What they don't have is the ability to do the correlative science that we can do here at the NIH. To overcome that we've set up a very in-depth infrastructure of getting blood drawn at INOVA, spun down and frozen there, and ultimately couriered over to the NIH, Monday through Friday.

These are labs that are drawn from the patient before the drug and then on days 1, 3, 5, 11, 15, 29 and ultimately day 60 hopefully as an outpatient. So setting up the infrastructure to get those bloods taken from those patients, frozen, processed, transferred to the NIH and then brought to our labs here where some of them are going to the research lab for future investigations, including looking at the neutrophil extracellular traps that I described earlier, and some of those going to our Department of Laboratory Medicine to look at secondary correlative outcomes, such as c-reactive protein and ferritins that are not part of routine clinical care that is occurring at Inova.

Those are the main two challenges. It's really trying to get patients to the Clinical Center and then having the ability to do the correlative science at INOVA by getting patient samples over here to the Clinical Center. It's taken a huge team for which we're very thankful to have working on this.

Barr: That's really great. In addition to all of your research, as you mentioned, you've also been very involved in caring for some of these COVID-19 patients at NIH. Can you talk a little bit about your experience? You had mentioned in an email that you helped care for one the first COVID-19 patients in NIH?

Strich: The care of patients with COVID-19 at the NIH actually began in March when we had our first patients who were transferred over to the NIH Clinical Center. It was really a fabulous collaborative effort between the National Institute of Allergy Infectious Diseases and the Critical Care Medicine Department to help care for these patients.

There's lots of challenges in terms of protecting the personnel who are taking care of these patients, doing it in a kind of biocontainment way, wanting to protect yourself with N95s [masks] and PPE [personal protective equipment]. Ultimately, these patients have the ability to get very, very sick and to get very, very sick quite rapidly.

In late March, we got our first patients that were transferred from another hospital, Suburban, over to the NIH Clinical Center. I went with our NIH fire department over to the ICU at Suburban to transfer our first patients over here to the NIH in the back of the NIH biocontainment ambulance and ultimately up to the Special Clinical Studies Unit at the NIH Clinical Center.

Over the course of the ACTT-1 study, which is what we were recruiting for, which was the remdesivir versus placebo study, we ultimately were able to recruit eight patients from local hospitals and care for them across different parts of the hospital, starting in the Special Clinical Studies Unit and ultimately expanding our ability to take care of more patients by opening a second unit in our intermediate care unit.

Barr: Did you feel prepared? Did you feel that any part of your training or background helped guide you because it was a very quick transition? A lot of protocols had to change very rapidly.

Strich: I think this was actually an opportunity for me as I trained in infectious diseases and critical care. SARS-CovV-2 is a disease that obviously is an infectious disease, a highly transmissible respiratory virus and also a disease that causes, unfortunately, a lot of patients to become critically ill and come to the intensive care unit.

From my perspective, it kind of fits into the wheelhouse of both of the types of training that I did here at the NIH Clinical Center. I did my ID training in the National Institute of Allergy Infectious Disease and then my critical care training here at the NIH Critical Care Medicine Department. From a clinical perspective I was prepared for this and actually this is kind of what I trained to do. Essentially in terms of these highly resistant or highly transmissible infections on a more practical level, we spent a lot of time in February preparing for these patients to come here. How are we going to do critical care up in a unit on the special clinical studies unit which typically doesn't do critical care as it provides a routine type of care for patients? We had to set up procedures for how we're going to put patients on life support if we needed to do that. How are we going to get ourselves donned into PPE and protective equipment if we need to rush in and see a patient? How are we going to do a procedure that may typically be a routine procedure on a patient if we have a gown on, two pairs of gloves, with decreased communication because the person who's helping you with the procedure also has a PPE and can't hear you? We spent a lot of time in February or early March training for this, preparing for this, and being ready for these patients to come over. Ultimately, when they came here, while it was something new for us, we were prepared, and we were ready, and we were excited to do it.

Barr: That's really great. What was it like to work under such intense circumstances? I'm sure it was very emotional, very nerve-wracking, and in some cases, it did not have a great outcome for some of these patients? Can you speak a little bit about the atmosphere and what it was like?

Strich: I think it was certainly nerve-wracking at first. I think that is a good way of putting it. I don't think we were particularly scared. We were scared for our patients. We were dealing with a disease that we didn't have any idea what the disease looked like. We didn't really have any proven therapies, so we were certainly scared for our patients.

But I think we were prepared in terms of our training to take care of those patients. Ultimately, I think it took a team to learn about this disease, to read about it, to communicate with other hospitals of what their experiences were about this disease, and really come together with a treatment plan for these patients that we were able to execute over our first couple patients. Then ultimately to learn to adapt

and change our strategy, so, as we've been through this pandemic, we have really changed the way we care for these patients.

A great example of that is two of our patients early on were put on mechanical ventilation early in their disease course because people commented about how quickly these patients becomecritically ill and need mechanical ventilation. That's what people were doing and people didn't want to wait till they got too sick to put them on mechanical ventilation. Now we have currently a patient in our ICU that probably back in March would have been intubated based on his clinical scenario and how much oxygen he is on, but we've learned—we're using other non-invasive ways of managing his oxygenation, including having him lay on his stomach to increase his oxygenation without having to go on a breathing machine. This allowed him not to be mechanically ventilated. We've learned a lot about this from where we are now in October versus where we were back in March.

Barr: That's really great. I think now we're going to go to more personal questions. How do you think COVID-19 has honed your skills as a medical and research professional?

Strich: The biggest thing is, I think, learning under the real time scenarios, so I'm just beginning my research career but I'm doing a clinical trial for the first time and doing it in the middle of a pandemic where everyone wants the answers not today but yesterday. We're trying to move as fast as we can, working seven days a week, staying up late at night, trying to get patients enrolled, learning about the disease, learning about the disease at the bedside, but also learning about the disease in the laboratory and see what we can do to hopefully improve the outcomes of these patients over time.

Barr: When you are not working, which sounds like it's almost all the time given the situation, what are some ways that you have relaxed and socially distanced your ways?

Strich: I try my best to spend time with my family. I have a young daughter and a young son at home and then my wife. Obviously, I do my best to make sure I do not bring COVID-19 home to the family which was clearly a concern early on in this disease. My mom was actually living with us at the time because we needed her down here to help us with the family. We're very grateful for that. Really, it's been a lot of Facetime. It's been a lot of Zoom. It's been a lot of no longer handshaking but using elbow bumps when we talk to people around our community. We've had a couple kind of social happy hours with everyone sitting at the end of the driveway; we ultimately just kind of stay with a close-knit group of

friends and family who are practicing safe precautions who you feel comfortable being around outside. Just trying to stay away from indoor restaurants and things like that. We haven't been out to eat at all since probably February. At this point, just trying to meet with people in a safe way.

Barr: Have there been any personal opportunities that have risen due to the pandemic?

Strich: I think just being able to be involved with all the research. The COVID-19 research, I think, is really high-profile research. There's really a lot of opportunities. I think that's been the biggest thing. The other thing is I think that COVID-19 and SARS-CoV-2 virus—we talk about this immune dysregulation—I think that there's a lot that we're going to learn from this virus about the immune system that ultimately can be translated back in the future to other diseases that haven't had significant progression in terms of their clinical understanding in quite some time. One of those would be bacterial sepsis—obviously a bacterial infection where the body becomes dysregulated in its immune response. There's lots of overlap between what we're learning with COVID-19 disease and sepsis. One future opportunity is taking all of these principles that we've learned about the treatment of COVID-19 and the pathogenesis of this disease and translating it to other diseases down the road in the future. Right now, we're certainly focused on getting through COVID-19. We're right in the middle of it and we're not through at all yet. We're still waiting for the vaccine. We're waiting for more effective therapies but ultimately, I think there'll be a time to take what we've learned from this disease and apply it to other diseases. This will be an opportunity in the future.

Barr: Definitely. So, what do you most look forward to doing when the virus subsides?

Strich: Going out to eat is the biggest thing and just being able to see some friends more regularly. I haven't been able to travel very much. I think that's really the biggest thing. Just a little more freedom.

Barr: We all agree. Was there anything else that you would like to share either as a scientist or as a person who's living through this pandemic?

Strich: No, I think I'm just grateful for the opportunity to talk to you today, to tell you about the studies that we're doing. One thing to mention is, I said this earlier, there's a huge team behind all the work that we're doing here, getting the study up and running with our collaborators in the National Heart Lung and Blood Institute, at INOVA, in the Critical Care Medicine department, and then the behind-the-scenes work in the laboratory that's happening also. Just really grateful for the opportunity to work with all these really outstanding colleagues and collaborators.

Barr: It's true people often don't realize all the work that goes behind all these clinical trials. Well, thank you very much and I wish you the best of luck on your research and, of course, thank you for caring for all these patients.

Strich: You're welcome.