Behind the Mask Interview with:

Lisa Rider, M.D.
Head and Senior Clinician, Environmental Autoimmunity Group, Clinical Research Branch, National Institute of Environmental Health Sciences (NIEHS)

Frederick Miller, M.D., Ph.D.
Scientist Emeritus, Environmental Autoimmunity Group, Clinical Research Branch, NIEHS

Adam I. Schiffenbauer, M.D.
Staff Clinician, Environmental Autoimmunity Group, Clinical Research Branch, NIEHS

Interviewed by Gabrielle Barr, Archivist, Office of NIH History and Stetten Museum, National Institutes of Health
November 21, 2022

Barr: Good afternoon. Today is November 21, 2022. My name is Gabrielle Barr, and I'm the archivist at the Office of NIH History and Stetten Museum. Today I have the pleasure of speaking with three scientists at NIEHS [National Institute of Environmental Health Sciences] who have been a part of doing COVID-19 research: Dr. Lisa Rider, Dr. Frederick Miller, and Dr. Adam Schiffenbauer. Thank you all for being with me and I look forward to hearing more. So my first question is, will you please explain why COVID-19 was such a concern for those with arthritis and other rheumatic diseases.

Miller: Want to start with that, Lisa?

Rider: Okay. I think that for patients with rheumatic disease, an autoimmune disease, that there's a history of having challenges with viral infections, both viral infections triggering disease, as well as disease flare-ups later in the pandemic. There was a concern for these patients that their disease may flare up if they got sick with the virus. [There was also a concern that many of them [who] are on immunosuppressive medications, would not be able to effectively fight off the virus. There was a lot of research on that topic as well.

As we went on into the pandemic, there became different concerns. it became apparent that, of course, once the vaccine became available, we had similar concerns for the vaccines with these patients. Would they have flare-ups of their autoimmune disease when they received these vaccines? Would they be able to effectively respond to these vaccines and be protected, given the immunosuppressant medications that they were receiving?

But then, I think, also with this particular virus, it became apparent that there were a number of immune-mediated and autoimmune sequelae of the viral infection itself. There were clotting syndromes due to autoantibody formation. There were patients who developed anti-interferon antibodies and therefore couldn't mount an interferon response and had very high mortality. [There were] other sequelae [such as] MIS-C in children [multisystem inflammatory syndrome in children], a febrile illness that clearly had a number of endothelial autoantibodies. I think that became an overwhelming concern: What was the autoimmune response in these patients with underlying autoimmunity or autoimmune predisposition as well?

Barr: Will you introduce the aims of the COVID-19 Global Rheumatology Alliance?

Rider: I just want to see if Fred or Adam had anything to add to that, though.

Miller: No, I think that that's a very good summary.

Schiffenbauer: I think we started off with concerns about increased risk of catching infections through the immunosuppressive medications and ineffective responses to those infections, risk of flares, and then more into the virus as a risk factor for disease overall. Then the vaccines having the same questions as they came out.

Barr: Definitely. Will you all introduce the COVID-19 Global Rheumatology Alliance and discuss a little bit about how it came into being and who the constituents of this group were because it was not just researchers?

Rider: Sure. The aims of the COVID-19 Global Rheumatology Alliance, I think, were similarly to understand about the risks of the infection in patients with rheumatic diseases and how they were faring with the infection and then later with the vaccines, very similar. I think they still have a registry going on to see how patients are doing with the infection, especially in patients with lupus right now. The COVID-19 Global Rheumatology Alliance really started as a multinational group of researchers and patients. They had a lot of support and backing from the major rheumatology societies, like the American College of Rheumatology and the European League Against Rheumatism, and many other societies. They're about 100 [or] 150 different societies and patient support organizations that support their work. They did a lot of their work through both physician registries and through patient registries —they had a lot of contacts in different patient organizations of these different diseases, all different rheumatic diseases throughout the world. [They] did a lot of gathering of patient data through social media and online surveys. They got large numbers of patients participating.

We got involved with them because we thought that it would be good with the concerns we had to study some issues related to the virus and what it was doing with patients with autoimmune disease. And we initially were very interested in looking at environmental factors that patients were exposed to in their different geographic areas, whether those were altering the infection in different places in patients with rheumatic diseases. We were initially going to do a project with them on that, but we were not funded by the ITAC [NIH Intramural Targeted Anti-COVID-19 Program] proposal for that project.

We stayed in touch with them. We did team up with them when they turned away from doing more studies on registries and the infection to trying to do studies about the vaccine response and attitudes toward vaccination in patients with rheumatic disease. They were launching a study on how the vaccine was going for patients with all different rheumatic diseases. We decided to look a little bit more on the immune-mediated side of the vaccine adverse-event question, and work with them specifically on that.

Barr: Can you speak a little bit more about this very large online international study that you introduced, a little bit more about it in general, in detail, and then a little bit more about your continued work that looked at the frequency of and risk factors for disease flare-ups following COVID-19 vaccination in patients with systemic rheumatic diseases?

Rider: They [the COVID-9 Global Rheumatology Alliance] were the ones that launched the survey. We did work with them to put in questions about the autoimmune disease flare-ups and about development of new autoimmune diseases. We tried to look at patients' responses to other vaccines—and we did use some of that data in this questionnaire and our analysis of that data about [whether] patients had a flare-up of their autoimmune disease with the vaccine. But there were other questions we asked about the response to other

vaccines. We really didn't capture the right data to be able to look in depth at any of the other vaccines, other than how patients tolerated the other vaccines, and was that a factor in how they responded to this vaccine.

They had a first study that they did on the vaccine adverse events, which I participated in, and just a general report after a few thousand patients had taken the vaccines. Then we waited a few more months for this study where we had more than 11,000 participants at this point. We would get data dumps from them. Their data was pretty clean, but we had to work on cleaning the data further and then analyzing with our group, specifically looking at some of these questions. We were able to tease out a few variables. There's no control group in these studies. They're very careful about saying that [with] the conclusions that can be drawn, and there may be biases in who participates. Without a control group, we can't know for sure if these are definitive factors. So we're really comparing things relative to other groups. Here we compared different disease groups relative to patients with rheumatoid arthritis or patients who flare compared to those who didn't. It's a relative analysis, and it brings up some possible associations that need further confirmation.

Barr: Can you talk a little bit more about some of these results and perhaps shed light on why certain disorders—I thought it was interesting that lupus had a higher instance of flaring up than in those with rheumatoid arthritis—and why AstraZeneca may have a higher flare-up than other types of vaccines? I thought that was really interesting. And do you know the underlying mechanisms about maybe why?

Rider: Well, this flare-up with lupus—I think this wasn't the first study that found that. There were a few other studies published around the same time that also were seeing a little bit of a signal with lupus. We put in some thought as to why this might be the case. It could be that, in lupus, there is quite a bit of type 1 interferon production. Maybe the vaccine itself, particularly the mRNA vaccine, might be activating toll-like receptors [and] that might even augment that interferon response further, leading to an increase in disease activity. That might be one of the ways that might be happening, if this finding is real. That might be some of the reason they're going on to this registry study with lupus now.

The AstraZeneca vaccine had been associated with some thrombotic autoimmune events and autoimmune thrombocytopenia. That might be why some patients may have more problems with that vaccine. Again, there's that predilection toward more autoantibody responses. It's hard to know for sure. Of course, we feel these findings need confirmation, but this would be some of the thoughts behind what might be with this data.

Barr: Are there any other differences?

Miller: There are a lot of differences, of course, in the different types of patients here in terms of potential baseline medications they might be taking, in terms of their underlying disease activities, in terms of the different organ systems involved, and so on [such as] the different immunogenetics that relate to developments of these diseases and potentially might impact how [patients] would respond to vaccines. There are possible explanations that we couldn't explore in this study given that we don't have any of that data collected.

Barr: Are there certain aspects of this study that you'd like to delve further into, if possible?

Miller: Well, there are a lot of limitations in what we could do since we wanted to keep these questionnaires relatively short, of course, given that there are participants that would be potentially unable to do long questionnaires, given their disease and their levels of capacity. It was a very short study in many ways. I think there were a lot of other questions we wanted to ask and we proposed at one point, but [the Alliance] thought

these were too many for us to be able to accommodate in this particular study. I don't think at the moment we have other plans, but Lisa [Rider], there is an ongoing study you mentioned that is still trying to collect some other information here. I'm sure others are probably doing studies that we're not aware of that might be trying to ask some of these questions.

Barr: Can you speak a little bit about how your group at NIEHS is contributing to Dr. Mariana Kaplan at NIAMS [National Institute of Arthritis and Musculoskeletal and Skin Diseases] on her work on the effects of the vaccine and infection on systemic rheumatic diseases?

Schiffenbauer: Sure. We've been very excited to collaborate with Dr. Kaplan, who's really looking at this across a group of different autoimmune disorders, bringing in patients with several different diseases to get more of a detailed analysis, particularly from the biological sample standpoint of what's going on with them. We've been helping [Kaplan's group] in terms of looking at myositis as a disease, particularly the pediatric version and the adult versions of the idiopathic inflammatory myopathies. [We're] trying to understand what the important questions are there. So not every disease gets the same criteria for how you look at it. So what is active disease or a flare in lupus may not be the same as what is active disease or flare in dermatomyositis or juvenile dermatomyositis. [We're] sorting on how those sorts of measures would go together, so we can get a better idea of how people's disease activity is across the board, and then try to get these patients in so we can really get the numbers to look at these in a more robust manner across disorders.

Barr: That's very interesting. Do you have any idea of, to date, how the actual disease COVID-19 has affected the flare-ups of your patients, and how Long COVID has affected your patients?

Rider: I think, anecdotally, we haven't heard too much about problems with flare-ups of disease. Maybe Dr. Schiffenbauer can speak further on that. I think we have definitely heard from a few patients who seemingly temporally to have developed their myositis following COVID infection, particularly, and without other explanations for that. So we have been trying to enroll those patients in our natural history study or in Dr. Kaplan's study. We don't have large numbers of these patients, but a few. It's something that we're trying to look into further—about their immune responses and those aspects.

Miller: The overall good news is these are relatively rare events. We don't see a large number of disease flares. It's a very small percentage, and we don't see a large number of cases of autoimmune diseases developing after the vaccines. I think that's the positive news to give to people.

Schiffenbauer: I think it's very rare that we're seeing these people and [we're] really looking carefully. It's easy when you have COVID and you have symptoms at the time to put the two together. But really sorting out in these patients whether they may have had disease beforehand [and it] just became more noticeable because they had mild weakness, and now they have more extreme weakness because they have COVID on top of it; or they are in isolation and have to do a lot more things for themselves than they normally would [because] someone might help them so they're just noticing it now versus new onset—we certainly have seen that—and whether this is an environmental risk factor, and whether it is unique. If it wasn't going to be a COVID infection that led to this, would it have been the next season's flu or some other activity that these people may have been engaged in and simply COVID got there first before other environmental factors in that particular individual.

Long COVID is something we're all concerned about that's impacting people. I think there's a lot of great research being done at NIH on that now and lots to come out of our colleagues over at the National Institute of Aging looking at this, and other groups. It's not something we've seen as a particularly different problem, anecdotally, from the patients we've seen compared to the general population. But certainly numbers and

understanding long COVID overall will help in terms of sorting this out more and what it means both acutely—which I think we're probably still in the time frame of acute for most people—to really long-term, when we look at responses later on.

Barr: Will you share about how you've been balancing your new COVID-19 project with your other projects, and how COVID has affected the operations and priorities in your lab?

Rider: Sure. I think during the height of the pandemic, the NIH Clinical Center had shut down for most admissions to the Clinical Center and shut the outpatient clinics, especially when viral transmission levels were high and prior to our having vaccines available. So we really refocused our work during this time. First of all, we had an ongoing FDA IND [Investigational New Drug] clinical trial for treatment of calcinosis [deposition of calcium in the skin, subcutaneous tissue, muscles, and visceral organs] in patients with juvenile and adult dermatomyositis, and that was the one study that Dr. Schiffenbauer led that we did keep open. He could speak in a minute to how we worked that out.

But I think we really had to rework a number of our protocols to try to work with people from their homes and not try to see them all at the Clinical Center, as we had in years past. [We] really tried to rework it so we could see a number of people by telehealth visits, in addition to having them enroll from home. So in other words, we would previously send people to their local physician to enroll, but now we were looking to even do it a different way—through telehealth. We made a lot of changes with our IRB [Institutional Review Board] protocols, getting IRB approval for these new processes and trying to continue our enrollments through this remote process.

During the height of the pandemic, we really tried to minimize staff coming to the office and also being in at overlapping times. We would try to strategize so that we could scan things to people who were working from home. They could handle them from home and on Zoom or Teams. Some of us would come in, or we tried to stagger when we were each in the office, to do different things. We couldn't be in somebody's room at the same time. For example, to examine a patient, we would have to take turns and stretch things out over longer periods of time. I think during the pandemic, we were also more focused on this COVID research. This study with the COVID-19 Global Rheumatology Alliance was a big focus at that time. We're continuing to work with Dr. Kaplan on her study at this time, but Adam [Schiffenbauer] could speak more to this point as well.

Schiffenbauer: I think, as Dr. Rider said, our group has been very proactive about a lot of this. Even before COVID, we were doing telehealth visits out in North Carolina with Dr. Miller, which was very exciting. [We were] using equipment that now probably looks archaic, but at the time it was cutting-edge equipment. We have done offsite enrollments with patients through their home physicians, but not necessarily by themselves. This led to a very rapid change in how we practiced everything across the board in terms of seeing our patients remotely. What did that mean? How did we organize that? Figuring out what outcome measures you can do remotely with the patient when you're talking about weakness and you can't touch them or push on their muscles or look at their rash maybe as closely as you would like. How do you adjust everything you've been doing for the past decade to be done in a completely new manner and make it so you can use that along with past data?

As Dr. Rider said, we had patients who still came into the Clinical Center for our drug study, which was one of the few studies open here. That had all sorts of other issues that arose with having patients here. One, our knowledge changed quickly; This was an area where the science was evolving at a minimum, day-to-day, if not hour-to-hour and that meant new regulations, new rules about who could come, who could go, what we knew about the right ways to isolate people, where they could come from. That had implications for how we brought

patients here. There were patients who tested negative for COVID a day or two before they came in and would show up, test positive for COVID, and have to go into isolation, for up to a few weeks. Our entire team would have to rally about changing their schedules around at the last minute and sorting everything out and make heroic efforts to accommodate these patients, who also ended up being here for two weeks longer than they expected, which is a large amount of time. International travel was incredibly complicated, with visas and changing rules. Then local travel, airplane cancellations, flight cancellations, people getting COVID, having to delay at home or here, or isolate somewhere. It was a very much an increased logistical effort to take care of these patients, to do what we did before, and to make sure that the team was safe and secure when we did it, that we had the right safety gear, and that we had the backup coverage.

Dr. Rider and I used to see patients together in an examination room all the time. We didn't do that for years as part of COVID, which meant the patient's time also got doubled. Instead of seeing two of us at the same time, they had to see one, then the other. But [it was] just to avoid that risk of having a medical team where we got exposed to virus and then everybody was out. [We were] doing that across our other personnel as well, so that we were sure that we always had people around who could fill things in as we were looking at these patients who were here.

Barr: That's really hard. Is there anything that you all thought that you learned during the pandemic that you would apply to other situations? Or you realized about yourself?

Rider: I think some of the most important lessons of the pandemic were flexibility; also just allowing us to stretch in new ways; really prioritize that patient safety and our safety are number one of importance; and that we can get our work done in very creative ways and work together to solve these problems. I think that was the most important takeaway of the pandemic at the end for our group.

Miller: I also think that the technology advances that occurred so quickly allowing us to do telemedicine and telecommunications—like we're doing right now, for example—were all important, probably positive developments in many ways that will impact how we work in the future as well. This expands to other meetings that will be taking place across the world, of course, and the use of hybrid meetings now that will allow us to do both in-person and telecommunications-type meetings at the same time, which will be a major change in how we do business in the future.

Schiffenbauer: Yeah, and I think questioning how we do things. Really shaking up everything at once may not be the ideal plan. Looking at lots of how things have been done for a long time, and really having to critically think about every aspect of it and how it changes is hard. But I think it leads to changes that are often good, not just in the moment, but maybe good overall in terms of efficiencies or better way to do things, or safer ways to do things. That sort of questioning of the status quo to optimize things, I think, was very helpful.

Barr: In addition to being scientists, you are also people who've been living through the pandemic this past two and a half years. What have been some personal opportunities and challenges that COVID-19 has presented to you all?

Rider: Well, I can start. Dr. Schiffenbauer spoke about the need to be sure that we weren't both infected with COVID at the same time and take extra precautions. Otherwise, we wouldn't have anybody to take care of the patients. I think that really just still extends. I think we both continue to be very careful in our personal lives about how we approach things and try to stay safe and try our best not to become infected with the virus,

because it would create some inconvenience to our patients and to our team. That continues to be part of our lives.

I think also maybe, as Fred [Miller] mentioned, the opportunity to connect with people, both professionally and personally, a bit more through longer distance through these new technologies, is definitely something that I've been able to enjoy. I think COVID-19 maybe slowed life down a little bit. It made us refocus a little bit more at home, at least at the beginning of the pandemic. I'm taking time myself to try to get a walk in almost every day that I can, and just take it a little bit slower. I think that was one of the opportunities from the pandemic.

Miller: The COVID-19 epidemic had incredible impacts on our society in general and on individuals in particular. I think we've all been rethinking our priorities, rethinking our life goals. Our wishes and our future plans have all been impacted, of course, by the pandemic. And again, I think it allows us to maybe, as Lisa [Rider] said, refocus our life perhaps a bit [and] think about what are really the most important things to us. What are the things that mean the most to us? Should we be prioritizing those perhaps even more in the future, and rethink our daily activities based upon those new priorities? It certainly had that impact on me.

Schiffenbauer: I agree with Dr. Rider. I'm on the side of less social interactions and a lot of being very careful about where we are with the infections. On the other side with the technology, I think we've had the opportunity to meet and work with a lot of people we may not have had the chance to before, to listen to lectures and talks from people all over because they're now virtual and everyone's available, and to collaborate in ways that-may not have been done. Certainly, there's advantages to having people in person, in those one-on-one interactions with human beings in a single room talking to each other, but there are people who probably I wouldn't have gotten a chance to meet with or talk to from all over the world had we not entered a world of virtual meetings where that's what we did on a regular basis

Barr: Is there anything else that anyone wants to share either about their COVID-19 work or experiences? [No one answers.] Well, in that case, I just want to thank you all very much for all that you have done during the pandemic, and I wish everyone continued success and health. I found your work very, very interesting, because I myself have rheumatoid arthritis, and so your research is really relevant to me. So I wanted to say thank you for all the work that you've been doing.

Rider: Thank you very much.

Miller: We thank you for this opportunity to be a part of the history of the NIH.

Schiffenbauer: Thank you.

Barr: Hope you all have a happy Thanksgiving.

Rider: You too.

Miller: Same to you.

Rider: Thank you so much.

Barr: Bye.

https://pubmed.ncbi.nlm.nih.gov/35460240/
https://pubmed.ncbi.nlm.nih.gov/34493645/